

# Associating demographic, clinical, and radiological presentation of HIV patients with TB and other co-infections in KPK, Pakistan

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## ABSTRACT

**Background:** The human immunodeficiency virus (HIV) afflicts the immune system by annihilating the white blood cells. The infection of HIV can alter the epidemiology and clinical profile of tuberculosis (TB) in patients suffering from co-infection. The objectives of the current study were to demographically and retrospectively analyze the data of HIV-infected patients admitted to different hospitals at KPK, Pakistan, and elaborate the key radiological and clinical differences in HIV positive patients with various co-infections and their effect on the CD4 level. **Methodology:** Initially, 1057 patients with HIV admitted to different hospitals of KPK were assessed for clinical presentation, co-infections, and their correlation with CD4 level. The data of patients, including date of hospital registration, weight, gender, diagnosis, age, and therapy, were obtained using a specifically designed Performa. In addition, sputum test of HIV patients was also conducted for screening of TB. **Results and Conclusion:** Our main findings are that HIV makes TB more severe such that CD4 count cell reduces to a level of 82-120 (killer stage). The incidence of HIV is two times greater in the males of the population under study. Young, single, and illiterate males were more affected by HIV and TB due to sexual contact and injecting intravenous drugs by contaminated syringes. Radiography was abnormal and pulmonary TB was common in HIV-positive TB patients. Co-infection of HIV and TB significantly reduced CD4 cells level in patients. The majority of HIV patients were Afghan refugees or those who came to Pakistan for better treatment.

**Key words:** Tuberculosis, HIV, AIDS, CD4 level

## INTRODUCTION

Tuberculosis is a long-term infectious disease caused by the bacteria *Mycobacterium tuberculosis* bacillus (Koch bacillus), whose major features include a predilection for lung parenchyma and dissemination from person to person through inhalation of a microorganism containing particles<sup>1</sup>. Tuberculosis is one of the most common infections associated with HIV infection<sup>2</sup>. Other research among HIV-positive TB patients shows that tuberculosis is a frequent opportunistic infection in HIV-positive individuals, with a significant frequency of pulmonary and extrapulmonary tuberculosis, as well as complex clinical presentations<sup>3</sup>. Clinical symptoms, sputum smear testing for acid-fast bacilli (AFB), tuberculin skin test, and chest radiography are used to diagnose pulmonary TB in most impoverished countries<sup>4</sup>. AIDS was first recognized in 1981; AIDS had a significant impact on the global TB issue as it changed its epidemiology and made containment more challenging<sup>5</sup>. In 2019, around 38 million individuals were living with HIV/AIDS worldwide<sup>6</sup>. There were 36.2 million adults and 1.8 million children (15 years

old). Tuberculosis affects over 2 million individuals per year, and management methods are vulnerable to early detection, drug resistance, and the socioeconomic conditions<sup>7</sup>. Infection with the human immunodeficiency virus (HIV) is a major risk factor for disease progression in those who have already been infected with the bacillus. While the likelihood of an infection developing to TB illness in immune-competent persons is 10% throughout their lifetime, it is likely to be 8 to 10% in HIV-negative infected individuals annually<sup>8</sup>. Furthermore, it is the earliest and most serious consequence among HIV-positive people, occurring before other public diseases. Clinical and radiographic differences between HIV-positive and HIV-negative individuals with tuberculosis have to be identified in studies. According to the World Health Organization (WHO), 4.4 million persons worldwide have dual infections with tuberculosis and HIV, with almost 80% of these people living in various areas<sup>9,10</sup>. One-third of all HIV/AIDS patients are also infected with *Mycobacterium tuberculosis*<sup>11</sup>. HIV is making the TB epidemic considerably eviler and has been the only significant factor de-

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termining the increased number of TB cases. In HIV-positive patients with CD4 counts > 200, radiographic discoveries are seen as infiltration and cavitations in upper lobes similar to tuberculosis in HIV-negative persons<sup>12</sup>. In HIV-positive patients with CD4 sum < 200 mediastinal adenopathy and pleural effusion are common, which is the same as the condition seen in HIV-negative patients with primary infection<sup>13-15</sup>. With molecular epidemiologic methods, it is proved that the presence of adenopathy does not necessarily represent primary infection, but it might probably be due to immunodeficiency<sup>16</sup>. About 5% of HIV-positive patients have normal radiography despite positive patients' sputum culture<sup>17</sup>. Severity in HIV lead to interest to study more about HIV and its co-infections, which result to sort out many co-infections caused by HIV accept TB that includes people with HIV are disproportionately impacted by viral hepatitis; about one-third of HIV patients are co-infected by either HBV or HCV, that can result in long-term illness and mortality<sup>18</sup>. The second most important co-infection is malaria HIV infection had an unpredictably enormous relationship with the effect of *Falciparum* malaria in a region of unstable transmission<sup>19</sup>. Diarrhea is also a general complication of HIV infection; 30-90% of patients with AIDS suffer from diarrhea at some point of their illness and detection of etiologic agents<sup>20</sup>. The goal of the current research was to demographically and retrospectively analyze the data of HIV-infected patients admitted to different hospitals at Peshawar and Kohat, KPK, Pakistan. The key radiological and clinical differences in HIV-positive patients with various co-infections and their effect on CD4 levels were also elaborated.

## MATERIAL AND METHODS

### Ethical Approval of the study

The Department of Zoology at Kohat University of Science and Technology in Pakistan, the Department of Microbiology at Khyber Medical University in Peshawar, Pakistan, the Department of Microbiology at Shaheed Benazir Bhutto Women University in Peshawar, Pakistan, and the AIDS control program in KPK gave approval for the study.

### Study zone and sample collection

The study was conceded out of different hospitals in Khyber Pakhtunkhwa, Pakistan, including Khyber Teaching Hospital, Hayatabad Medical Complex, Kohat Medical College, and Lady Reading Hospital Peshawar. Initially, a retrospective study was conducted on HIV patients admitted to these hospitals

for 8 years (January 2012 – December 2019). The medical and microbiological records were analyzed. The data of patients, including date of hospital registration, weight, gender, diagnosis, age, and therapy, were obtained using a specifically designed Performa. Sputum test of HIV patients was also conducted for screening of TB.

The sample was collected from KPK hospitals according to 5 different categories.

- **Gender:** About 1057 patient samples were taken according gender-wise and divided into 4 categories i.e., male, female, children, and infants
- **Age:** Out of 1057, samples were taken out according to age gap that includes: 10-20, 21-30, 31- 40, and > 40 and were studied
- **Area:** According to area-wise distribution, patients were divided into the following groups: KPK, Fata, Attock, Afghani, and Prisoners
- **Demographic:** The demographic and clinical variables were set, which were common in KPK that include mainly fever, weight loss, cachexia, diaphoresis, and diabetes in 1057 patients.
- **CD4 Level:** The level of CD4 cells in HIV patients concerning co-infection was also determined.

The BD FACS System was used to acquire absolute CD4+ levels in the sample<sup>21</sup>.

### Sputum

It includes a sputum test on which microscopy, Ziehl-nelson staining, and Elisa was performed. Out of 1057 sputum models, 153 were obtained directly from the patients in a clean and sanitized sputum vessel and correctly labeled. Then, all of the samples were taken to the Molecular Parasitology and Virology Lab, Department of Zoology, Kohat University of Science and Technology's AIDS Control Program in KPK, Kohat, for TB diagnosis.

The yellowish part was trawled out from the sputum flask and placed on a slide with an uneven stick. The material was uniformly spread on a slide in an approximate area of 2cm-1cm for comprehensibly drying. The smear was then completely dried and heat fixated.

### Ziehl-Neelsen staining

The prepared slides were then placed on the staining chamber, which contained Carbol Fuchsin, and left for about 5-10 minutes. For fixing, the heat was provided through a spirit lamp. After cooling of slides, a little amount of decolorizing agent was added. It

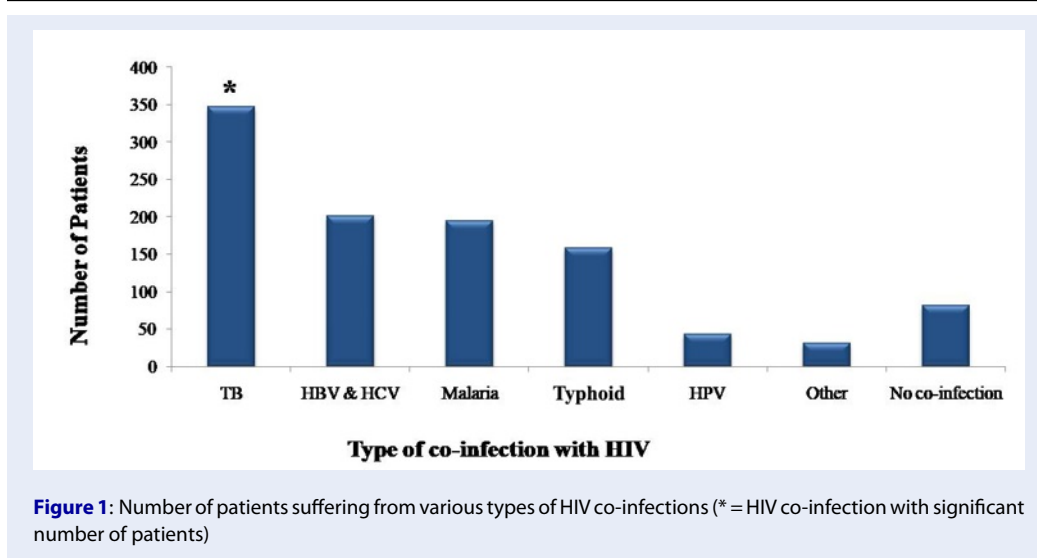


Figure 1: Number of patients suffering from various types of HIV co-infections (\* = HIV co-infection with significant number of patients)

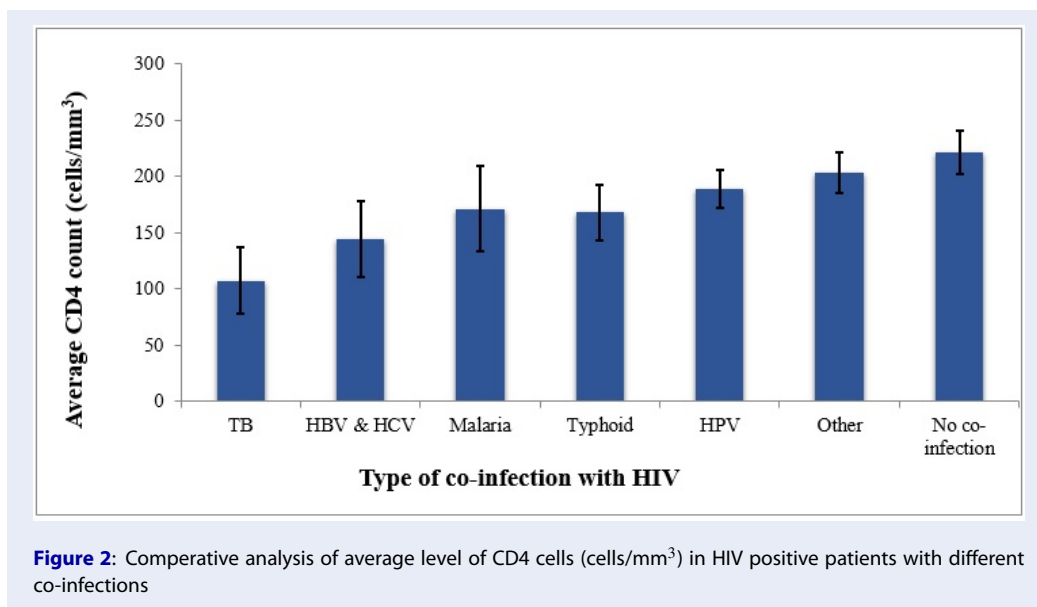


Figure 2: Comparative analysis of average level of CD4 cells (cells/mm³) in HIV positive patients with different co-infections

was followed by washing with usual tape water. The slide was once again dipped in the second box, which contained methylene blue for 5-10 minutes. The prepared smear was observed under the oil immersion microscope at 10xs, 40xs, and 100xs and acknowledged with the regular images. Slides with red rods against the blue background show the existence of *Mycobacterium* (TB).

**Statistical Analysis**

Constant data was characterized by the mean (SD), while the frequency and percentages represented categorical data. The mean of continuous variables in three classes is compared using a one-way ANOVA. In

categorical factors, the chi-square was used to determine the mean. Significant was described as a P value of 0.05 or less. Microsoft Excel 2016 and the SPSS statistical program version 15 were utilized to analyze the data.

**1. RESULTS**

**Retrospective, Demographics and Clinical analysis**

The retrospective analysis revealed that a total of 1291 HIV patients were admitted to hospitals of KPK from January 2012 – December 2019, out of which 234 were eliminated due to lack of data, who were not willing to

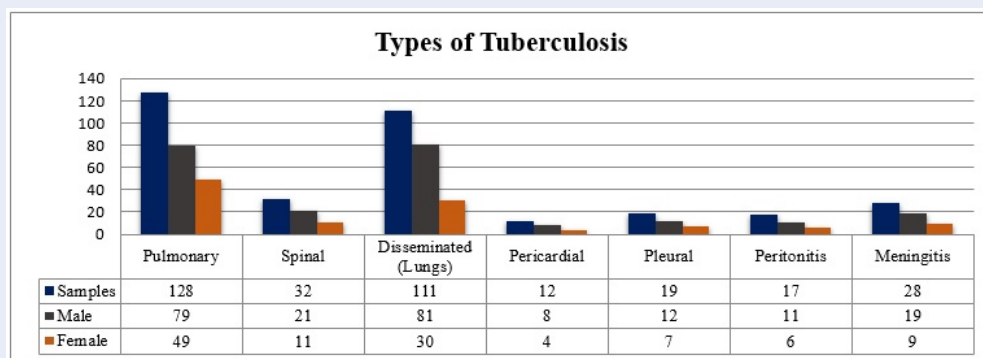


Figure 3: Radiological and sputum test results representing involvement of different sites of TB among HIV positive TB patients

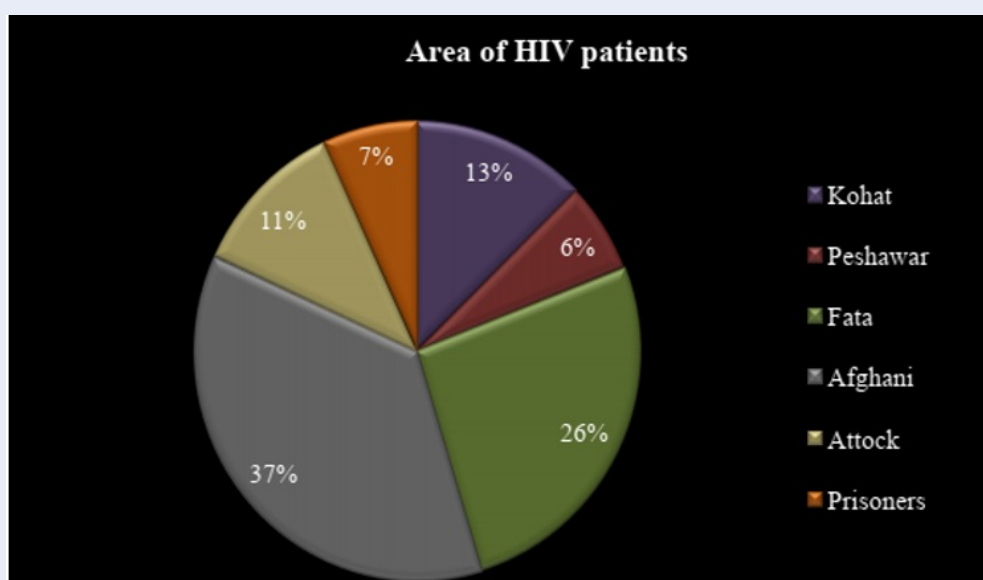


Figure 4: Regional and populational representation of HIV infected patients

participate, or patients with age less than 15. Of 1057 HIV patients, 74.14% were males with ages ranging between 21- 30 (77.95%). The majority of the infected patients were single and illiterate (79.71% and 78.33%, respectively). In the current study, injecting drugs by utilizing contaminated syringes and sexual relationships with the infected person were the significant viral transmission route in patients (Table 1). The clinical and demographic analysis of HIV patients with several types of co-infections revealed that the HIV patients with TB were more suffering from shortness of breath, fever, and cough as compared to other patients. 15% of HIV patients with co-infections other than TB had Cachexia, and 39% had developed Diaphoresis, whereas patients with co-infection of HIV

+ TB were more exposed to Diaphoresis and Cachexia (47% and 36%, respectively). 33% HIV positive TB had a history of TB, while 78% of patients were addicted to drug abuse and 33% to alcohol which became the cause of TB and HIV (Table 2).

### HIV and Co-infections

In the present study, the investigation of HIV patients for co-infections revealed that out of 1057 HIV patients, 82 were not suffering from any co-infection, while the majority of patients were suffering from a co-infection of HIV + TB (347) and HIV + HBV or HCV (201). A significant number of HIV patients with a co-infection with Malaria and typhoid were also detected (198 and 155, respectively). Few im-

**Table 1: Demographic and retrospective analysis of HIV patients admitted to various hospitals of Peshawar and KPK**

Total	Samples	Male	Female	Male %	Female %
	1057	784	273	74.17%	25.83%
<b>Age</b>					
15-20	110	71	39	64.55%	35.45%
21-30	458	357	101	77.95%	22.05%
31-40	321	231	90	71.96%	28.04%
>40	168	125	43	74.40%	25.60%
<b>Marital Status</b>					
Married	406	328	78	80.79%	19.21%
Unmarried	478	381	97	79.71%	20.29%
Divorced or Widow	127	48	79	37.80%	62.20%
Not known	46	27	19	58.70%	41.30%
<b>Education Status</b>					
Illiterate	526	412	114	78.33%	21.67%
Primary	288	206	82	71.53%	28.47%
Junior	173	112	61	64.74%	35.26%
Senior	47	38	9	80.85%	19.15%
College	14	9	5	64.29%	35.71%
Unknown	9	7	2	77.78%	22.22%
<b>Transmission route</b>					
Sexual route	218	180	38	82.57%	17.43%
Injecting drug	524	443	81	84.54%	15.46%
Blood transfusion	112	73	39	65.18%	34.82%
Unknown	203	88	115	43.35%	56.65%

immune compromised HIV patients had typhoid and HPV infections as well (Figure 1).

### Level of CD4 cells

Individuals infected with HIV had  $221.3 \pm 19.3$  cell/mm<sup>3</sup> CD4 cells, however, in HIV + TB co-infected patients, the amount of CD4 cells dropped to the lethal stage ( $107.4 \pm 29.2$  cell/mm<sup>3</sup>). Co-infection of HBV and HIV or HCV also significantly reduced the CD4 level in infected patients ( $144.7 \pm 33.6$  cell/mm<sup>3</sup>). Patients suffering from AIDS and co-infection of typhoid, HPV, and Malaria also negatively affected CD4 levels in patients (Figure 2).

### Types of Tuberculosis in HIV patients

In current research work, out of 1057 HIV patients, 347 suffered from a co-infection of HIV + TB. The radiological analysis revealed that lungs were more damaged as most HIV patients were suffering from pulmonary TB and disseminated (lungs) TB (128 and 111, respectively). Spinal and meningitis TB was also detected among patients (32 and 28, respectively) (Figure 3).

### Area of HIV patients

According to figure 4, most HIV patients were Afghan refugees or those Afghans who came to Pakistan for better treatment in hospitals of KPK (386, 37%). Similarly, in the area of Pakistan near to Pak-afghan border, FATA (Federally Administered Tribal Areas) was

**Table 2: Comparative representation of clinical analysis and medical history of HIV positive TB patients and HIV patients with other co-infections**

Variable	HIV+TB	HIV+ other Co-infections
Fever	83%	64%
Cough	77%	67%
Short Of Breathes	67%	48%
Weight Loss	66%	60%
Diaphoresis	47%	39%
Cachexia	36%	15%
Symptoms >2 Week	40%	67%
Diabetes mellitu	9%	15%
Sputum	73%	70%
Alcohol Use	33%	30%
Immuno-compromised	17%	30%
Other Drug User	78%	47%
History Of Tb	31%	11%
Time Duration (Months)	8-11	14-18

also affected with HIV (278, 26%). 13% of patients belonged to Kohat, and 11% from Attock, KPK, Pakistan. In addition, due to homosexual interaction among prisoners, 7% of prisoners were suffering from AIDS.

### DISCUSSION

Pakistan is one of four Asian nations where HIV prevalence has increased over the last decade. Over the same time frame, the number of new HIV infections increased from 14000 in 2010 to 22000 in 2018, resulting in a 368 % rise in HIV-related fatalities with male domination<sup>22,23</sup>. Even though HIV is largely confined to specific populations, Infections have previously emerged in the general population<sup>24,25</sup>. The present study has comprised a total of 1057 HIV patients. Males made up 74.14 % of the 1057 HIV patients, with most of them aged 21 to 30. The patients that were infected were mostly unmarried and uneducated. Another group of causes that could be leading to an elevated risk of HIV contamination in terms of sexual activity is social tension and a high prevalence of drug addiction<sup>26</sup>. Previous accounts of recurring sexual assault, early age suicide attempts, and clinical distress indicate psychological stress<sup>27</sup>. While Vertical propagation might potentially be a factor, it is generally thought that the parenteral spread of HIV by the misuse of needles in healthcare settings is to blame for the epidemic<sup>25,28</sup>. In the current

investigation, the most common viral transmission routes in patients were injecting drugs using contaminated syringes and having sexual connections with infected people (Table 1). Shortness of breath, fever, and cough was more common in HIV patients with tuberculosis (TB). HIV patients with TB were more likely to develop Diaphoresis and Cachexia. 33% of HIV-positive TB patients had a history of TB, while 78% were addicted to drugs and 32% to alcohol (Table 2). The rise of HIV has increased the global burden of tuberculosis. As a result, HIV infection greatly raises the risk of contracting active tuberculosis. In the fight against tuberculosis, the T-lymphocyte subset is crucial. Ironically, HIV depletes CD4+ T-lymphocytes, making co-infected people more susceptible to tuberculosis<sup>29</sup>. Co-infection with HIV and tuberculosis (TB), also known as the "cursed duet," is becoming a significant public health issue in Sub-Saharan Africa, where 70-80 % of HIV-positive patients also have TB<sup>30</sup>. The immunological, virological, biochemical, and elastographic responses of patients co-infected with HIV and HBV or HCV and their development and prognosis are not well understood<sup>31,32</sup>. Cirrhosis and end-stage liver disease occur as a result of insufficient immune responses to the hepatitis viruses in co-infected individuals<sup>33-35</sup>. HIV co-infection is related to hepatitis flaring after ART treatment and is responsible for a greater risk of death than HCV or HBV infection only<sup>36,37</sup>. The analysis of HIV patients for

co-infections indicated that 82 had no co-infections, while most patients had a co-infection of HIV + TB (347). A significant proportion of HIV patients were also found to have co-infections with HCV, Malaria, and Typhoid (Figure 1).

The level of CD4 cells decreases when an HIV infection progresses and exposure to any other co-infection<sup>11,38</sup>. In different articles, it has been noted that clinical and radiologic manifestations in HIV patients are different reliant on the level of immunity suppression in different patients<sup>12,39,40</sup>. In such a way, in different reports, it has been pointed out that in CD4 counts of less than 200, atypical manifestations are present and also called killer stage<sup>12,41,42</sup>. In the current study, individuals infected with solely HIV had  $221.3 \pm 19.3$  cell/mm<sup>3</sup> CD4 cells, whereas HIV + TB co-infected patients had  $107.4 \pm 29.2$  cell/mm<sup>3</sup> CD4 cells (Figure 2).

Unlike other HIV-associated adaptive infections, tuberculosis can strike at any stage of immunosuppressant patients, while its occurrence up to level rises in patients with extra immunosuppression<sup>43,44</sup>. Pulmonary tuberculosis is diagnosed using prolonged signs, chest X-ray differences, sputum smear, and culture, but approximate diagnosis can be challenging because clinical and radiological results can be non-specific, particularly in HIV-positive patients. However, in resource-limited nations, most pulmonary tuberculosis diagnoses are made using chest X-rays and clinical features<sup>45,46</sup>. Most HIV patients had pulmonary TB and disseminated (lungs) TB (128 and 111, respectively). Therefore the radiological investigation indicated that the lungs were more affected. HIV Patients with spinal and meningitis TB was also detected (Figure 3).

The chest radiography detection of pulmonary tuberculosis in advanced HIV infection is apparently unlike associated with persons with fewer severe immunosuppression<sup>47</sup>. The lower lobe of the lung, middle lobe of the lung, interstitial fluid, lungs exudates, and pleural effusion and intrudes is mutual, and cavitations are very few<sup>48,49</sup>. However, other radiographic findings, such as pleural effusion, were less prevalent in our HIV-positive individuals than other studies, suggesting that atypical radiological presentations of PTB are common in HIV-positive participants.

The use of inhaled and injected drugs, multiple sex habits, men who have sex with men (MSM), and interaction with sex workers may increase the risk of contracting HIV among refugees and foreigners<sup>50,51</sup>. According to a Pakistani survey, 54% of migrant men engage in unprotected sex, with only a handful using condoms<sup>50,52</sup>. A connection between HIV infection

and population displacement (refugees and internally displaced people) from conflict/war-affected areas has been identified<sup>50</sup>. The present study shows that most HIV patients were Afghan refugees or Afghans who had come to Pakistan for better treatment at KPK institutions (386, 37%) (Figure 4). Similarly, HIV was found in FATA (Federally Administered Tribal Areas) in Pakistan near the Afghan border. AIDS was also infected 7% of prisoners due to homosexual activity. MSM is believed to account for 5–10% of all new HIV infections worldwide<sup>53</sup>. Evidence suggests that this population is more susceptible to HIV infection<sup>53,54</sup>. It is important to remember that Pakistani culture does not support the presence of MSM, which may explain why data on MSM and STDs in the country are scarce.

## CONCLUSIONS

It is concluded from the current study that young single and illiterate males were more affected by HIV and TB, due to sexual contacts and injecting intravenous drugs by contaminated syringes. As compared to other co-infections, the patients with co-infection of TB and HIV were more affected demographically and clinically, such as high fever, shortness of breathing, Diaphoresis, Cachexia, and extreme cough. Radiography was abnormal and pulmonary TB was common in HIV-positive TB patients. Co-infection of HIV and TB significantly reduced CD4 cells level in patients (less than 82-124, killer stage). The majority of HIV patients were Afghan refugees or those Afghans who came to Pakistan for better treatment in hospitals due to unprotected sex or homosexuality. HIV adversely affects the human body's immune system and opens pathways for other microbial infections; therefore, it is a risk factor for TB and the cause of HBV, HCV, typhoid, diarrhea, HPV, and many more.

## LIST OF ABBREVIATIONS

- HIV Human immunodeficiency virus
- TB Tuberculosis
- CD4 Cluster of Differentiation 4
- AFB Acid-fast bacilli
- AIDS Acquired Immune Deficiency Syndrome
- WHO World Health Organization
- HCV Hepatitis C Virus
- HBV Hepatitis B Virus
- HPV Human Papilloma Virus
- MSM Men who have Sex with Men
- STDs Sexually Transmitted Disease

## ETHICAL APPROVAL

Kohat University of Science and Technology in Pakistan, Shaheed Benazir Bhutto Women University in Peshawar, Pakistan, Khyber Medical University in Peshawar, Pakistan, and the national AIDS and TB control program in KPK gave ethical approval to the study.

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## CONFLICT OF INTEREST

The authors declare that they have no competing or conflict of interest.

## AUTHORS CONTRIBUTION

All the authors contributed equally in the conceptualization of the study, data collection and analysis, manuscript writing, and final approval.

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