Clinical predictors of low CD4 count among HIV-infected pulmonary tuberculosis clients: A health facility-based survey

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Objectives. The study aimed to determine the clinical and laboratory predictors of a low CD4+ cell count (<200 cells/μl) in HIV-infected patients with pulmonary tuberculosis (PTB).

Design and setting. A prospective cohort study on HIV-positive patients with smear-positive PTB attending an outpatient clinic in Zimbabwe.

Participants. Consecutively consenting HIV-positive adults, aged 18 years and over, who had positive sputum smears for acid-fast bacilli and were naïve to both antituberculosis drugs and ART.

Interventions. Baseline CD4+ cell count, full blood count, functional status using the Karnofsky Performance Status (KPS) score and body mass index (BMI, kg/m^2) were determined for all participants. Univariate and multiple logistic regression analyses of the data were done.

Results. Of the 97 participants recruited, 59 (61%) were females. The overall mean age was 34 years (standard deviation (SD) 8). The median CD4+ cell count was 104.5 cells/μl (intraquartile range (IQR) 41 - 213 cells/μl). Patients with pleuritic chest pain were less likely to have a low CD4+ cell count than patients who did not (odds ratio (OR) 0.2; confidence interval (CI) 0.03 - 0.8). The following were statistically significant predictors of a CD4+ cell count of <200 cells/μl: BMI <18 kg/m^2 (OR 3.8; CI 1.2 - 12), KPS <54.4 (OR 3; CI 1.1 - 12) and haemoglobin concentration <8 g/dl (OR 13; CI 1.8 - 533).

Conclusions. HIV-infected sputum-positive PTB patients presenting with a BMI <18, KPS <54.4% and haemoglobin concentration <8 g/dl should have early initiation of ART since they are more likely to have a low CD4+ cell count, whereas those presenting with pleuritic pain are less likely to have a low CD4+ cell count.

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Tuberculosis (TB) remains one of the most important opportunistic infections among HIV-infected patients. Diagnosing pulmonary TB (PTB) has become problematic because HIV-positive patients tend to be smear negative and smear microscopy is the first line of diagnosis in people suspected to have TB.[1] It is estimated that more than 50% of HIV-infected patients will develop TB in their lifetime, and the annual risk of developing TB if HIV infected is 10%.[2] Various studies have shown high mortality rates in HIV-infected TB patients in resource-limited settings.[2] HIV infection increases the risk of acquiring TB, alters the clinical presentation of TB and reduces overall survival.[3,4] High mortality rates in these patients have been attributed to severe immunosuppression as measured by CD4+ cell count, and to lack of antiretroviral therapy (ART).[5]

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One of the major challenges in resource-limited settings is clinical identification of HIV-infected TB patients who have sufficiently low CD4+ cell counts to merit early initiation of ART without the aid of expensive and not readily available CD4+ cell count tests. Being able to predict who might have a low CD4+ cell count would assist in the prioritisation of TB patients for ART and thus prevent initiation of ART when it is not yet indicated, an important advantage given that ART is a lifelong commitment.

Materials and methods

A prospective cohort study was done on consecutive consenting participants presenting at Beatrice Road Infectious Disease Hospital (BRIDH), Harare, Zimbabwe, and meeting the following inclusion criteria: age 18 years and over, HIV positive, sputum smear positive for acid-fast bacilli (AFB), and naïve to both ART and TB treatment. Patients with symptoms and signs suggestive of PTB were asked to produce two sputum specimens (one spot and an early-morning sample) for AFB microscopic examination using the Ziehl-Neelsen (ZN) staining technique. Participants with positive smears for AFB were offered HIV testing and counselling. HIV tests were done using the Determine (Abbott Laboratories; sensitivity 100%, specificity 98.60%) and Capillus (Trinity Biotech, Ireland; sensitivity 97.8%, specificity 99.7%) rapid test kits. Baseline laboratory tests including a CD4 cell count (Partec Cyflow SL3) and full blood count (Sysmex KF21) were done.

Socio-demographic data, medical history and the findings on physical examination were recorded using a standardised data collection tool. The baseline body mass index (BMI, kg/m^2) and Karnofsky Performance Status (KPS) score were determined at enrolment.

A sample size of 80 at 95% confidence interval (CI) was calculated using Epi Info version 6, assuming a population of 10 000 TB cases per year. Data were analysed using STATA version 8 (College Station, Tex., USA).

Baseline characteristics were reported as means (standard deviation, SD) or medians (intraquartile range, IQR). Univariate and multivariate analyses were conducted to determine clinical predictors of a low CD4

cell count (<200 cells/μl). The participants were stratified into two groups on the basis of their CD4 cell count (<200 and ≥200 cells/μl). The groups were compared using chi-square testing. Most variables were reported as odds ratios (OR) with 95% confidence intervals (CI).

The study was approved by the Medical Research Council of Zimbabwe (MRCZ). Permission to conduct the study at BRIDH was obtained from the Director of the Harare City Health Department.

Results

Demographic description of the study population

A total of 97 participants who were both sputum positive for AFB and HIV positive were recruited into the study, 59 (61%) being females (Table I). The overall mean age was 34 years (SD 8 years). The females were younger (mean age 32 (SD 7) years) than the males (36 (SD 9) years). A quarter of the participants were widowed. The mean number of years of formal education was 10 (SD 2) years.

Clinical and laboratory characteristics of the study population

The baseline clinical characteristics (Table II) showed an overall mean BMI of 18.7 (SD 2.6), with the mean for the males BMI 18.7 (SD 2.3) and that for the females 18.7 (SD 2.9). The mean KPS score was 54.4% (SD 11.9%). Baseline CD4 counts were available for 96 participants, and of these 69 (72%) had a CD4 count of less than 200 cells/μl. The median CD4 count was 104.5 cells/μl (1st quartile 41; 3rd quartile 13). The overall mean haemoglobin concentration was 9.4 (SD 2.1) g/dl.

Having a low haemoglobin concentration (<8 g/dl), a low BMI (<18) and a low KPS score (<54.4%) were found to be predictive of having a low CD4+ cell count (<200 cells/μl), with ORs of 13, 3.8 and 3, respectively (Table III). Bivariate analysis using a clinically significant KPS score cut-off of 50% and a CD4 cell count above or below 200 cells/μl did not show statistical significance. All participants with a KPS score of less than 50% had a CD4 cell count of less than 200 cells/μl. Patients with pleuritic pain were less likely than those who did not to have a CD4+ cell count less than 200 cells/μl (OR 0.2; CI 0.03 - 0.8; p=0.01).

The overall multiple logistic regression model showed that a significant variation in CD4 cell count was explained by the haemoglobin concentration, BMI and KPS score (p=0.0004). In this model, only haemoglobin remained significantly related to low CD4 cell count (p=0.01). KPS score and BMI were individually not significantly related to CD4 cell count (p=0.5 and 0.1, respectively).

Table I. Baseline demographic characteristics of the participants (*N*=97)

Variable	*N*
Mean age (yrs) (mean (SD))	
Overall	34 (8)
Females	32 (7)
Males	36 (9)
Gender (*N* (%))	
Female	59 (61)
Male	38 (39)
Marital status (*N* (%))	
Single	16 (17)
Married	45 (46)
Divorced	12 (12)
Widowed	24 (25)
Formal education (yrs) (mean (SD))	10 (2)

Table II. Baseline clinical and laboratory characteristics of the study participants

Variable	
Weight (kg) (mean (CI))	
Males	55.7 (47.9 - 63.5)
Females	50 (42 - 58)
Height (m) (mean (CI))	
Males	1.73 (1.65 - 1.81)
Females	1.64 (1.58 - 1.70)
Body mass index (mean (CI))	
Overall	18.7 (18.2 - 19.2)
Males	18.7 (17.9 - 19.5)
Females	18.7 (17.9 - 19.5)
Karnofsky Performance Status score (%) (mean (CI))	54.4 (52 - 56.8)
Haemoglobin (g/dl) (mean (CI))	9.4 (8.9 - 9.8)
CD4 count (cells/μl) (median (IQR))	104.5 (41 - 213)

Discussion

In resource-limited hospitals like most district hospitals in Zimbabwe, where CD4 machines and other complicated diagnostic equipment are not available, good clinical acumen is required to predict which patients are likely to have a low CD4 count (<200 cells/μl) and therefore need early initiation of ART.

The demographic characteristics of the participants, of whom 61% were women, compare well with the general population of people living with HIV/AIDS seeking other Zimbabwean public-sector ART services, of whom two-thirds are women.[6] HIV/TB co-infection has been shown to be associated with significant weight loss.[7,8] The BMI was used as an indicator of the nutritional status of the participants. Although the males were heavier and taller than the females, the mean BMI was the same for both sexes. The overall mean BMI (18.7 (SD 2.6)) was just above the lower limit of the normal range (18 - 25). A BMI of <18 was found to be a significant predictor of a low CD4 count. Apart from suggesting severe immunosuppression, these results imply that nutritional support should form part of the comprehensive package of care of HIV-infected TB patients.

Studies have shown that HIV-infected TB patients are more likely to present for the first time with moderate or severe illness.[7,8] We used the KPS score to quantify the degree of disease progression at the first visit to the hospital. The mean KPS score was low (54.4%) at enrolment. A KPS score of 60% refers to requiring occasional assistance but being able to care for most of one's needs, whereas a score of 50% refers to requiring considerable assistance and frequent medical care. The data were therefore analysed using a clinically relevant KPS cut-off point of 50%. This KPS score (<50%) was chosen as it is also easy to operationalise at a health care level setting. Although statistical significance could not be established (Table III) because there was no participant with both a low KPS score (<50%) and a CD4 cell count >200 cells/μl, we can safely conclude that a KPS score <50% is predictive of a low CD4 count (<200 cells/μl) in HIV-infected patients with PTB.[9] HIV-positive patients who present with PTB and a low KPS score (<50%) should therefore be started on ART early.

It has been noted that people with advanced HIV commonly suffer from anaemia because of their inability to produce adequate levels of erythropoietin. Anaemia has been shown to be associated with high mortality, as it appears to be an indicator of advanced

Table III. Clinical predictors of low CD4 count at TB diagnosis (*N*=96)*

Characteristic	CD4 <200/µl (*N*=69)	CD4 ≥200/µl (*N*=27)	*p*-value	OR (95% CI)
Presenting complaints				
Cough	61	25	0.58	0.6 (0.1 - 3.4)
Night sweat	54	20	0.70	1.3 (0.4 - 3.9)
Musculoskeletal pains	34	8	0.08	2.3 (0.8 - 6.9)
Confusion	8	0	0.06	N/A
Chronic diarrhoea	3	0	0.27	N/A
Bloodstained sputum	5	4	0.25	0.4 (0.1 - 2.5)
Pleuritic pain	44	24	0.01†	0.2 (0.03 - 0.8)
Chronic tiredness	55	20	0.55	0.4 (0.1 - 2.5)
Medical examination findings				
Pyrexia (axillary temperature >37°C)	31	11	0.71	1.2 (0.4 - 3.3)
Shortness of breath	42	15	0.63	1.2 (0.5 - 3.4)
Abdominal distension	3	0	0.27	N/A
Herpes zoster scar	9	5	0.49	0.7 (0.2 - 2.8)
Oral ulcers	6	1	0.40	2.5 (0.3 - 118.2)
Oral candidiasis	14	3	0.29	2 (0.5 - 12.0)
Weight loss >10% body weight	11	5	0.76	0.8 (0.2 - 3.4)
KPS <54.4%	45	10	0.01†	3 (1.1 - 12)
KPS <50%	12	0	N/A‡	N/A
BMI <18	34	6	0.01†	3.8 (1.2 - 12.0)
Laboratory				
Haemoglobin <8 g/dl	22	1	0.00†	13 (1.8 - 532.5)

* 1 patient did not have initial CD4 results.

†Statistically significant at 5% significance level.

‡Statistical significance could not be determined owing to a zero frequency in one of the cells.
N/A = not applicable.

HIV disease.[10] In our study, HIV-positive PTB patients with a haemoglobin concentration of <8 g/dl had a low CD4 count (OR 13; CI 1.8 - 533). This wide CI is likely to have resulted from the small sample size following stratification of the haemoglobin data. The above finding implies that any HIV-positive pulmonary TB patient with a haemoglobin concentration <8 g/dl should be started on ART.

Although the overall multiple logistic regression model including haemoglobin, BMI and KPS score as the explanatory variables was significant (p=0.002), the haemoglobin concentration was the only variable (p=0.01) that remained significantly related to the low CD4 count.

Chest pain is commonly present in HIV-infected TB patients.[5] The presence of pleuritic pain was significantly associated with a higher CD4 count (>200 cells/µl), and this is in keeping with the World Health Organization recommendation that initiation of ART can be deferred in patients with TB adenitis and pleural disease as long as there is good response to TB therapy.[11]

HIV-infected PTB patients presenting with a BMI <18, a KPS score <50% and a haemoglobin concentration <8 g/dl merit early initiation of ART. These results suggest that clinicians in resource-limited settings can identify HIV-infected PTB patients who will need to be started on ART early using a clinical assessment alone without the aid of a CD4 cell count result. These findings should assist clinicians to prioritise as well as to scale up the provision of ART in resource-limited settings where TB is generally widely prevalent.

The study had the following limitations: we enrolled only smear-positive PTB participants in an urban tertiary-level facility, where patients have relatively easy access to care. The study participants therefore comprised a highly selected population and may not be representative of all PTB/HIV co-infected patients.

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All the authors participated in the conception and design of the study, analysis and interpretation of the data, drafting and revision of the manuscript, and approval of the final version for publication. CN led the study implementation and data collection team, and RAK, FEO and CEN monitored the study implementation and data collection process. The authors declare that they have no conflict of interests.

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