


# The Impact of Absolute CD4 Count and Percentage Discordance on Pneumocystis Jirovecii Pneumonia Prophylaxis in HIV-Infected Patients

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## Abstract

Current guidelines suggest that HIV-infected patients should receive chemoprophylaxis against *Pneumocystis jirovecii* pneumonia (PJP) if they have a cluster determinant 4 (CD4) count  $<200$  cells/mm<sup>3</sup> or oropharyngeal candidiasis. Persons with CD4 percentage (CD4%) below 14% should also be considered for prophylaxis. Discordance between CD4 count and CD4% occurs in 16% to 25% of HIV-infected patients. Provider compliance with current PJP prophylaxis guidelines when such discordance is present was assessed. Electronic medical records of 429 HIV-infected individuals who had CD4 count and CD4% measured at our clinic were reviewed. CD4 count and percentage discordance was seen in 57 (13%) of 429. Patients with CD4 count  $>200$  but CD4%  $<14$  were significantly less likely to be prescribed PJP prophylaxis compared with those who had CD4 count  $<200$  and CD4%  $>14$  (29% versus 86%; odds ratio = 0.064, 95% confidence interval: 0.0168–0.2436;  $P < .0001$ ). We emphasize monitoring both the absolute CD4 count and percentage to appropriately guide PJP primary and secondary prophylaxis.

## Keywords

CD4 count, CD4 %, *Pneumocystis jirovecii* pneumonia, prophylaxis

## Background

The absolute count of human helper T lymphocytes that express cluster determinant 4 (CD4) count is pivotal in the management of HIV infection and in determining immune function and serving as an indicator of when to start prophylaxis against opportunistic infections. Current guidelines<sup>1</sup> suggest that HIV-infected patients should receive chemoprophylaxis against *Pneumocystis jirovecii* pneumonia (PJP) if they have a CD4 count of less than 200 cells/mm<sup>3</sup> or a history of oropharyngeal candidiasis. Guidelines also recommend that persons with a CD4 percentage (CD4%) below 14% should also be considered for prophylaxis.<sup>1–3</sup> Physicians are often faced with a discordant CD4 count/CD4% pair. Previous studies of discordant CD4 count and CD4% have focused on how it predicts disease progression in HIV and how it influences outcomes on antiretroviral therapy (ART),<sup>4</sup> but no study has evaluated how such discordance affects provider compliance with current guidelines on PJP prophylaxis. This study was conducted to assess provider compliance with current PJP prophylaxis guidelines when discordance between CD4 count and CD4% is present.

## Methods

This study was a retrospective chart review of the electronic medical records of HIV-infected patients receiving care at Harlem Hospital's Infectious Diseases (ID) Clinic. Over 1000 HIV-infected patients receive HIV primary care in the hospital's ID clinic. Patient information from all visits is stored in an electronic database (Discoverer Plus). Records of HIV-infected patients who had absolute CD4 count and CD4% measured at the ID clinic during the study period July 2010 to April 2011 were reviewed. Patients with a CD4 count  $>200$  but a CD4%  $<14$  and conversely a CD4 count  $<200$  but CD4%  $>14$  were

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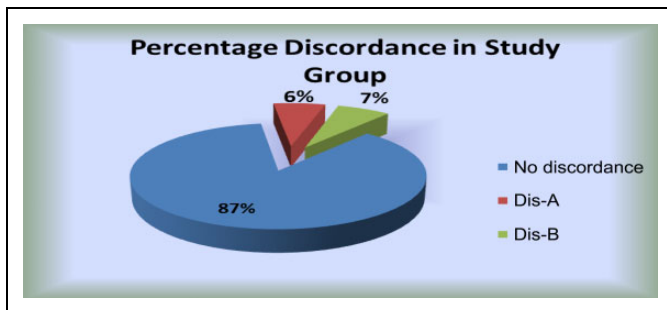
**Table 1.** Demographics of study population.

	Dis A, <sup>a</sup> n (%)	Dis B, <sup>b</sup> n (%)
Male	14 (63)	13 (45)
Female	8 (37)	16 (55)
African American	14 (63)	15 (51)
Hispanic	8 (37)	12 (41)
Caucasian	0 (0)	2 (7)
Total patients	22	29

Abbreviations: CD4, cluster determinant 4; Dis, discordance.

<sup>a</sup>Dis A—CD4 >200 and CD4% <14.

<sup>b</sup>Dis B—CD4 <200 and CD4% >14.

**Figure 1.** Percentage discordance in study group.

defined to have a CD4 discordance. Discordance A (Dis-A) included patients with CD4 count >200 and CD4% <14 and discordance B (Dis-B) included patients with CD4 count <200 but CD4% >14.

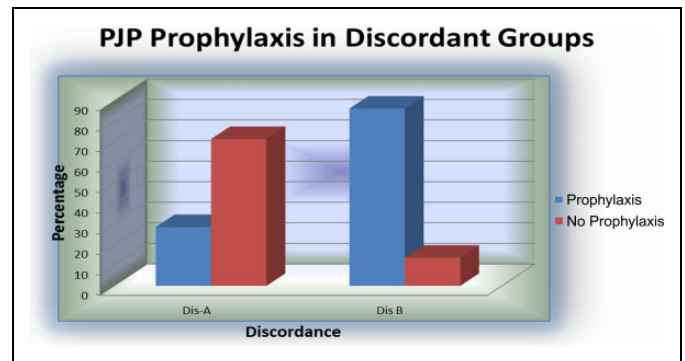
We reviewed whether patients with CD4 discordance were on PJP prophylaxis 6 months prior and 6 months after their CD4 count/CD4% pair in question was measured. Any form of PJP prophylaxis including trimethoprim–sulfamethoxazole (TMP-SMX), atovaquone, dapsone, and pentamidine was considered. Development of PJP, hospital admissions for respiratory illness other than PJP (eg, bronchitis and pneumonia), viral load, and ART were also assessed.

Odds ratios were calculated and  $\chi^2$  or Fisher exact test were used to assess associations for categorical variables. Statistical analyses were executed with SAS version 9.2 (SAS Institute, Inc).

## Results

A total of 429 HIV-infected patients had absolute CD4 count and CD4% measured at the ID clinic during the study period; 53% were male, 81% were black (non-Hispanic), 15% Hispanic, and 2% white (see Table 1). Absolute CD4 count and percentage discordance was seen in 57 (13%) of 429; 28 (6.5%) of 429 had Dis-A and 29 (6.7%) of 429 had Dis-B (Figure 1).

Use of PJP prophylaxis varied by the type of discordance (Figure 2). One hundred thirty-nine patients had CD4 percentage  $\leq 14\%$ , and 28 of these had Dis-A. Twenty (71.4%) of 28 patients with Dis-A were not on PJP prophylaxis; the 8

**Figure 2.** Pneumocystis jirovecii pneumonia prophylaxis in discordant groups.

(28.6%) of 28 patients on PJP prophylaxis all were receiving TMP-SMX. Two hundred ninety patients had a CD4% >14, and of these, 29 had Dis-B. Only 4 (13.7%) of 29 patients with Dis-B were not on PJP prophylaxis. Of the 25 (86.2%) of 29 patients on PJP prophylaxis, 6 were receiving atovaquone and 19 TMP-SMX. Patients in the Dis-A group were significantly less likely to be on PJP prophylaxis compared to patients in the Dis-B group ( $P < .0001$ , OR = 0.064, 95% CI: 0.0168-0.2436).

Seventeen (60.7%) of 28 patients in the Dis-A group were prescribed ART and 16 (55.2%) of 29 patients in the Dis-B were prescribed ART. History of oral candida was comparable in both groups, including 3 (10.7%) of 28 in the Dis-A group and 3 (10.3%) of 29 in the Dis-B.

Detectable HIV viremia was present in 87.5% in the Dis A group compared to 71.4% in the Dis B group. One patient in the Dis-A group on ART with a CD4 count of 680 cells/mm<sup>3</sup> (nadir CD4 count 289) and CD4% of 6% had been hospitalized with presumed PJP. No patient in the Dis-B group had PJP.

Three patients in the Dis-A group were admitted to the hospital for respiratory illnesses other than PJP, all of these patients were not on PJP prophylaxis. Ten patients in the Dis-B group were admitted for respiratory illnesses; 9 of these 10 patients were on PJP prophylaxis (7 on TMP-SMX and 2 on atovaquone).

## Discussion

The absolute CD4 count is pivotal in the management of HIV infection, as a marker of immune function and a determinant of when to start prophylaxis against opportunistic infections.<sup>1</sup> The absolute CD4 count is a product of the CD4% derived from flow cytometry and the complete white blood cell count and lymphocyte differential.<sup>5,6</sup> A gating strategy for identifying lymphocytes using CD45 fluorescence and side-scattering characteristics is available and is the preferred method for identifying lymphocytes accurately and reproducibly.<sup>7</sup> Unfortunately, multiple factors including but not limited to medications, chemotherapy,<sup>8</sup> steroids,<sup>9</sup> infections,<sup>10</sup> smoking,<sup>11</sup> alcohol,<sup>12</sup> and diurnal changes<sup>13</sup> affect the absolute CD4 count, making the CD4% a less variable indicator.<sup>14</sup>

Although CD4 count and CD4% are highly correlated, these correlations are not perfect.<sup>4,5</sup> Discordance between CD4 count and CD4% has been well-documented in previous studies,<sup>4,15-18</sup> occurring in 16% to 25% of HIV-infected patients.<sup>17,18</sup> However, the clinical relevance of this discordance remains unclear.<sup>4</sup> Unfortunately, there is no standard definition for CD4 count and CD4% discordance, but our definition (Dis-A and Dis-B above) is similar to definitions used in previous studies.<sup>15,16</sup> In patients with HIV-1 infection, CD4 count predicts development of opportunistic illnesses and death due to AIDS.<sup>16-20</sup> On the other hand, other studies have found CD4% as predictive of the risk of clinical progression independent of CD4 count.<sup>17,18,21</sup> In a large study of 1020 asymptomatic HIV-infected individuals, the intrasubject coefficient of variation for CD4 count was 25% compared to 18% for the CD4%.<sup>22</sup>

In our study, we found a 13% discordance between CD4 count and CD4%. Based on our findings, it was obvious that most providers when faced with the clinical dilemma of a discordant CD4 count-CD4% pair tended to focus on the absolute CD4 count for PJP prophylaxis. One individual in the Dis-A group who was receiving ART with a CD4 count of 680 cells/mm<sup>3</sup> and CD4% of 6% had presumed PJP based on clinical symptoms and complete recovery after treatment with TMP-SMX. He was not on PJP prophylaxis. This emphasizes the importance of PJP prophylaxis for patients with such discordance. No patient developed presumed or confirmed PJP in the Dis-B group, but contrary to our expectation, more patients in this group were admitted for respiratory infections (10/29 patients, 9/10 patients were on TMP-SMX and 3 had confirmed bacterial infections). We expected TMP-SMX at a dose of 1 double-strength tablet daily to confer protection against some common respiratory bacterial infections.<sup>23,24</sup> Our study however is limited by the small number of patients with the CD4 count and percentage discordance and the lack of data on adherence to medications.

Some studies have suggested that primary pneumocystis prophylaxis may not be necessary for individuals who are virologically suppressed on ART with CD4 counts of 100 to 200, given the low incidence of PJP in this group.<sup>25,26</sup> Unfortunately, only 30% of the total estimated HIV-infected population in the United States are virologically suppressed.<sup>27</sup> *Pneumocystis jirovecii* pneumonia remains a major threat to HIV-infected individuals because of late HIV diagnosis and poor antiretroviral adherence.

A 1259-person study from France found that almost half of HIV-infected persons with newly diagnosed PJP had already entered HIV care, and three quarters of that group had started ART.<sup>28</sup> Provider knowledge and vigilance in all aspects of PJP prophylaxis is necessary in preventing *Pneumocystis pneumonia* in HIV-infected patients.

Guidelines currently recommend that PJP prophylaxis should be discontinued in HIV-infected patients who have responded to ART with an increase in CD4 count to greater than 200 cells/mm<sup>3</sup> for greater than 3 months.<sup>1,29-31</sup> It is not clear when to discontinue PJP prophylaxis after starting solely based on a CD4%, but in the studies<sup>29-31</sup> supporting the above

recommendation, most patients at the time of discontinuing prophylaxis had a CD4% greater than or equal to 14%.

## Conclusion

In this study, the use of PJP prophylaxis seemed to be determined more by the CD4 count than the CD4%. Although our study is based on a retrospective medical record review, it forms a platform for further studies to better understand the clinical relevance of CD4 count and percentage in determining PJP prophylaxis. We emphasize monitoring both the absolute CD4 count and percentage to appropriately guide PJP primary and secondary prophylaxis in accordance with current guidelines.

## Declaration of Conflicting Interests

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