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# Anemia among HIV-infected Individuals in South India

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## ABSTRACT

### Anemia among HIV-infected Individuals in South India

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*Objective:*
Although highly active antiretroviral therapy (HAART) resolves a significant proportion of anemia among HIV-patients in Western cohorts, outcomes may vary in developing countries, due to a higher prevalence of nutritional deficiencies, intestinal parasites, tuberculosis, and opportunistic infections. The purpose of this study is to describe the prevalence of, factors associated with, and influence of HAART on, anemia among HIV-infected individuals in South India.

*Methods:*
To examine factors associated with anemia, the first-recorded hemoglobin values for adults who visited an HIV tertiary care center in Chennai, India between January 1996 and April 2006 were collected (n=7069). Univariate and multivariate regression analyses were performed to examine associations between anemia and stage of HIV disease, co-morbidities, and medications. To examine the influence of HAART use on anemia on a smaller subset of patients (n=401), the mean of baseline hemoglobin values measured within 3 months prior to HAART initiation was compared to the mean of follow-up hemoglobin values collected between 3-12 months after HAART initiation. A similar analysis based on the time of AIDS onset was performed for a control group of patients with clinical/immunological AIDS who never received HAART (n=77).

*Results:*
The prevalence of anemia in the overall cohort was 40% by the WHO definition. While 22% of patients with CD4 counts >500 cells/μL had anemia, this increased to 60% for those with CD4 counts <100 cells/μL ($p<0.001$). In multivariate analysis, CD4 count <100 cells/μL, underweight body mass index, female sex, active tuberculosis, and lack of cotrimoxazole prophylaxis had significant associations with anemia. In the analysis of the influence of HAART on anemia, median baseline CD4 count and mean time to follow-up hemoglobin value were similar for both the HAART and control arms. For patients who initiated HAART, the mean baseline hemoglobin of 10.7g/dL significantly increased to 12.4g/dL during the year of follow-up ($p<0.001$). While 46.6% of patients

were not anemic at HAART initiation, this increased significantly to 78.1% during follow-up ($p<0.001$). Severe grades 3 and 4 anemia decreased from 12.5% to 2% for those on HAART ($p<0.001$). For the control arm of patients who never received HAART, the increase in mean baseline hemoglobin from 10.50 to 11.10g/dL did not reach significance ($p=0.06$). While the percent of non-anemic patients increased from 40.3 to 54.5% on follow-up in this group, this was not significant ($p=0.291$).

*Conclusion:*
Anemia is strongly correlated with the severity of immunosuppression in this population seen at an HIV tertiary referral center. Endemic malnutrition and tuberculosis further exacerbate the level of anemia. Anemia resolved in a large proportion of patients within the first year of HAART use. Therefore, antiretroviral therapy, nutritional supplementation, and aggressive tuberculosis treatment should be the cornerstones of anemia management in this setting. The high prevalence of anemia among patients with immunological AIDS complicates the roll-out of antiretroviral regimens containing zidovudine, a drug which may exacerbate anemia, and highlights the need for increased access to alternative nucleoside reverse transcriptase inhibitors in developing countries.

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## INTRODUCTION

Anemia is widespread in the general population of developing countries, especially among women.(1) In India, more than half of women are estimated to be anemic, and nearly one-fifth suffer from moderate or severe levels of anemia.(2) It is also one of the most frequent morbidities and the most common hematological complication associated with HIV infection, with rates increasing as the disease progresses.(3-5) Anemia has been shown to influence the natural history of HIV disease by accelerating the rate of disease progression and increasing mortality in both developed and developing country studies.(4, 6, 7) Conversely, survival time in HIV-infected individuals may be improved with recovery from anemia.(4) By causing symptoms of fatigue and exhaustion, anemia also has a major impact on the quality of life of people living with HIV (8, 9) and possibly even exacerbates poverty in communities with a high HIV prevalence.(10)

The pathogenesis of anemia in HIV-infected individuals is complex. While much of the burden is attributable to the anemia of chronic disease, nutritional deficiencies, opportunistic infections, malignancies, parvovirus B19, viral inhibition of hematopoetic stem cells, and medications (including antiretroviral therapy) also contribute to anemia in those with HIV disease.(11) In most cases, the etiology is multifactorial.(11, 12) In cohort studies from developed countries, risk factors independently associated with anemia in HIV-infected individuals included age, female gender, African-American race, low CD4 cell count, and drugs like zidovudine, fluconazole, and ganciclovir. Independently associated co-morbidities in these studies included *Mycobacterium avium*

complex, lymphoma, bacterial pneumonia, septicemia, oral candidiasis, and other hematological abnormalities (i.e., neutropenia and thrombocytopenia).(4, 7, 13)

When superimposed on already high levels of background anemia, HIV disease in developing countries may produce extremely high rates of anemia. Compared to the 20-60% percent prevalence of anemia found in U.S. and European cohorts of HIV patients,(4, 7, 13, 14) multiple studies of HIV-infected individuals from sub-Saharan Africa have found the prevalence of anemia ranges from 70-90%, though many of these studies were done in pregnant women or patients co-infected with tuberculosis.(6, 11, 15-17) Risk factors for anemia in these settings possibly vary from those in developed countries due to high rates of endemic malnutrition, helminth infections, malaria, and a different spectrum of HIV-associated opportunistic infections. For example, multiple studies have suggested that tuberculosis (TB), which is the second most common opportunistic infection in South India,(18) plays a major role in the etiology of anemia among HIV-infected patients in developing countries.(15, 19)

Multiple studies from developed countries suggest that use of highly active antiretroviral therapy (HAART) reduces the risk of anemia in patients with HIV infection and greatly improves hemoglobin values in many patients who are already anemic at the time of HAART initiation.(3, 7, 20-23) While these data from Western cohorts is promising, the beneficial impact of HAART on anemia may be diminished in developing countries, where nutritional deficiencies, intestinal parasites, malaria, tuberculosis, and the higher burden of opportunistic infections may deplete marrow reserves, resulting in persistence

of anemia despite viral suppression and reconstitution of the immune system. Few studies have examined HIV-associated anemia in developing countries, where the vast majority of HIV-infected individuals live, and no study has examined the impact of HAART on anemia in these settings. These questions are especially important in India, the country that currently has the largest population of people living with HIV.(24) Here we report the prevalence of, factors associated with, and impact of HAART on, anemia among HIV-infected individuals at an HIV/AIDS tertiary care center in South India.

## STATEMENT OF PURPOSE AND HYPOTHESIS

This study has three purposes:

1. To report the prevalence of anemia in the patient population of the largest private HIV tertiary care center in South India.

2. To determine clinical factors associated with anemia and the independent odds of having anemia with each of these factors.

3. To examine the impact of highly active antiretroviral therapy on anemia in this patient population.

For each of the purposes noted above, I suggest the following hypotheses:

1. Due to the impact of HIV disease, the prevalence of anemia in this clinic population will be higher than that found in the general South Indian population. It will also be higher than those found in most HIV-infected cohorts in Western countries (due to the higher level of baseline anemia in the Indian population). The prevalence of anemia will increase in patients with more advanced HIV disease, due to the higher burden of infections and malnutrition in patients with more advanced immunosuppression.

2. Multiple clinical factors will be associated with anemia in this cohort, highlighting the many etiologies of anemia in this patient population. While immunosuppression will be associated with anemia, malnutrition and tuberculosis will be more strongly associated with anemia in this cohort when compared to studies from developed countries.

3. There will be minimal or no resolution of anemia after HAART initiation in this patient population because the high burden of non-HIV-associated etiologies of anemia (malnutrition, helminth infection, TB) will reduce the hematological benefits of HAART.

## METHODS

*Setting and Patients*

The Y.R. Gaitonde Centre for AIDS Research and Education (YRG CARE) is a non-profit, non-governmental, HIV tertiary referral clinic in Chennai (formerly Madras), India, which has provided a continuum of care—including voluntary counseling and testing, outpatient, and inpatient services—to over 9000 patients since 1993 (Illustrations 1, 2, and 3). All patients are treated according to World Health Organization (WHO) guidelines for resource-limited settings.(25) YRG CARE has a 20-bed inpatient ward where patients are admitted for management of HIV-associated opportunistic infections and toxicities from antiretroviral drugs. While diseases not associated with HIV (e.g., malaria) are usually managed in other hospitals, YRG CARE sometimes admits patients for non-HIV related illnesses if they have been refused admission elsewhere due to their HIV status. While the majority of patients cared for at the clinic are adults, the clinic also holds a pediatric outpatient clinic every one to two months and manages children in the inpatient ward throughout the year.

YRG CARE has played a vital role in shaping India's response to the HIV epidemic. The founder and director of the clinic, Dr. Suniti Solomon, led the team that discovered the first cases of HIV in India in 1986. After managing HIV cases in Chennai's large government hospital, Dr. Solomon retired from government service to start the clinic in the early 1990s. In addition to patient care, YRG CARE has directed the development of sexual education programs throughout thousands of middle and high schools in the state of Tamil Nadu. The clinic has research affiliations with several major U.S. medical

schools, including Brown University and Johns Hopkins and is a research site for multiple NIH-funded clinical trials.

YRG CARE was one of the first medical centers in India to offer antiretroviral therapy to people living with HIV. While initially restricted to patients who could afford it, the availability of antiretroviral therapy has been expanded in recent years through programs funded by the United Nations Global Fund for AIDS, TB, and Malaria and AIDS Project Los Angeles, which subsidize therapy for poor patients. Since the initiation of free roll-out of antiretroviral therapy by the Indian government in late 2004, patients who cannot afford antiretroviral therapy and are not covered by subsidy programs are referred to government roll-out centers to receive therapy. Patients with access to therapy are advised to initiate these medications at CD4 cell counts <200 cells/μL or if there is a history of an AIDS-defining illness. Patients are followed up every three months or as clinically indicated. The majority of patients visiting the clinic come from the southern Indian states of Tamil Nadu and Andhra Pradesh, where surveys estimate rates of background anemia among women to be 57% and 50% respectively.(2)

Analysis was done using the previously validated YRG CARE HIV Observational Database,(26) This database is updated after every patient visit by trained research nurses who extract demographic and clinical details based on a standardized data collection form approved by YRG CARE's independent institutional review board. Data collected include demographic variables (age, sex, mode of HIV transmission), clinical assessments (new opportunistic infections and HIV-related co-morbidities), use of

antiretroviral medications, adverse events from antiretroviral medications, use of cotrimoxazole prophylaxis, and laboratory data (CD4 cell counts, hemoglobin values, and plasma viral loads, if available). Data is not collected on use of complementary and alternative medicines.

*In this study, data from the YRG CARE HIV Observational database is used to do two separate analyses. The first analysis uses cross-sectional data from a larger sample of patients to examine the prevalence of, and risk-factors associated with, anemia in the YRG CARE cohort. The second analysis uses a smaller sample of patients to examine the impact of HAART on anemia.* The methods for these two different analyses are described below.

*Prevalence of Anemia and Factors Associated with Anemia*

For the first analysis, patients who visited YRG CARE between January 1, 1996 and March 31, 2006, who were greater than 18 years of age at the time of enrollment for care at the clinic, and who had at least one hemoglobin value in the database were included. The analysis was performed using the first recorded hemoglobin value after the patient's enrollment for care at the clinic.

Anemia was classified by WHO criteria for both men and women: grade 0 or "non-anemic" (hemoglobin values ≥11 g/dL), grade 1 or "mild" anemia (9.5-10.9 g/dL), grade 2 or "moderate" anemia (8-9.4 g/dL), grade 3 or "severe" anemia (6.5-7.9 g/dL), and grade 4 or "life-threatening" anemia (<6.5 g/dL). For comparison with other studies,

anemia was also reclassified as hemoglobin values <12 g/dL for women and <13 g/dL for men as noted. Patients who had used triple drug antiretroviral therapy (ART) for at least one month prior to the date of the hemoglobin value were considered to be "on highly active antiretroviral therapy (HAART)," while those who used single or double drug ART for at least one month prior to the date of the hemoglobin were considered to be "on mono/dual therapy." Patients who never started ART or took it for less than one month prior to the hemoglobin value were considered to be "not on ART." Of note, the HAART regimen for nearly all patients at YRG CARE consists of stavudine or zidovudine + lamivudine + nevirapine or efavirenz, with more patients using stavudine and nevirapine over zidovudine and efavirenz, respectively, due to the lower cost of the former medications. Less than one percent of patients are taking other antiretroviral medications such as tenofovir, abacavir, or protease inhibitors. Patients who took cotrimoxazole prophylaxis for at least seven days prior to the date of hemoglobin value were considered to be "on cotrimoxazole." Most patients are initiated on cotrimoxazole prophylaxis at CD4 cell counts between 200-300 cells/μL when possible; however, since many patients initially only present for care when they have reached very advanced stages of immunosuppression, some are initiated on prophylaxis at lower CD4 counts.

Body mass index (BMI) was calculated as weight (kg) divided by height squared ($m^2$), and BMI values within one month prior to or after the date of the hemoglobin for a given patient were included in the analysis. "Underweight" was defined as a BMI less than 18.5 $kg/m^2$, "normal weight" as a BMI from 18.5 to 25 $kg/m^2$, and "overweight/obese" as a BMI of 25 $kg/m^2$ or greater. "Gastroenteropathy" included all cases of chronic

diarrhea, including confirmed diagnoses of cryptosporidium and *Isospora belli* infection. "Renal disease" included all patients with chronic renal insufficiency, end stage renal disease, and HIV nephropathy.

CD4 cell counts were included in the analysis if recorded in the two months prior to or after the date of the hemoglobin. Patients were considered to have the following diseases if any serological diagnosis was recorded prior to the date of the hemoglobin: hepatitis C virus infection, hepatitis B virus infection, and syphilis. All other relevant HIV-associated co-morbidities in the database were divided those considered to have chronic presentations and those with acute presentations. Diseases with acute presentation were included in the analysis if diagnosed within the one month prior to or after the date of the hemoglobin. This group consisted of the following: oral candidiasis, esophageal candidiasis, *Pneumocystic jiroveci* pneumonia (PCP), cryptococcal meningitis, cytomegalovirus retinitis, oral hairy leukoplakia, herpes zoster, herpes simplex, gastroenteropathy, bacterial pneumonia, bacterial meningitis, bacterial infections of the skin, immune reconstitution syndrome, and immune thrombocytopenia. Diseases with chronic presentation were included in the analysis if diagnosed within the two months prior to or after the date of the hemoglobin for a given patient. This group consisted of the following diseases: pulmonary TB, extrapulmonary TB, lymphadenopathy, ascites, and renal disease. The association of anemia with Kaposi sarcoma is not reported, since this neoplasm is very rare among HIV patients in India (likely due to the very low prevalence of human herpes virus-8 in the population). Only two cases of Kaposi

sarcoma from India have been reported in the medical literature, both among immigrants to India.

*Impact of HAART on Anemia*

The second analysis included patients who visited YRG CARE between January 1, 1996 and March 31, 2006 and who were greater than 18 years of age at the time of enrollment for care at the clinic. This sample was further restricted to patients who had been on HAART for at least three months and had not interrupted therapy for greater than 14 days within that time period. Further, all patients had to have a baseline hemoglobin value and at least one follow-up hemoglobin value. A baseline hemoglobin value was defined as any hemoglobin measured within the three months prior to, or within two days after, the date of HAART initiation. A follow-up hemoglobin value was defined as any hemoglobin value collected between the three to twelve months following the date of HAART initiation.

This sample of patients on HAART was compared to a control group of patients who had clinical or immunological AIDS but never received HAART. Almost all of these patients suffered from AIDS prior to the widespread availability of HAART in India, and therefore did not received HAART despite qualifying for the therapy on clinical or immunological grounds. Immunological AIDS was defined as any CD4 cell count $\leq$200 cells/μL. Clinical AIDS was defined as having an AIDS-defining illness as defined by WHO criteria. For these patients, a baseline hemoglobin value was defined as any hemoglobin measured within the three months prior to, or within two days after, the date

of diagnosis of clinical or immunological AIDS. A follow-up hemoglobin value was defined as any hemoglobin value collected between the three to twelve months following the date of diagnosis of clinical or immunological AIDS.

For both the HAART and control groups, baseline hemoglobin data was compared to the mean of all follow-up hemoglobin values. The definitions of anemia used are similar to those noted above for the analysis of anemia prevalence and associated factors.

*Statistical Analysis*

All statistical analyses were performed with SPSS software (version 10.0.5; SPSS, Chicago, IL). Continuous variables with normal distribution were summarized using mean and standard deviation (SD). For non-normal data, median and interquartile ratio (IQR) were used. Frequencies and percentages were calculated for all the categorical variables. Students t-test was used to compare the mean hemoglobins of the various CD4 cell count strata. Chi-squared for trend was used to determine significant trends in the percent of patients with a given grade of anemia at different CD4 cell count strata using Epi Info version 3.3.2, Centers for Disease Control and Prevention.

Univariate logistic regression was performed to understand the associations between age, sex , HIV-associated co-morbidities, CD4 cell counts, and patterns of medication use for non-anemic versus anemic patients. Bacterial pneumonia, bacterial meningitis, immune reconstitution syndrome, idiopathic thrombocytopenia, hepatitis B virus infection, and hepatitis C virus infection were not included in the univariate analysis due to small

frequency. A multivariate model was then built using forward stepwise techniques. Variables that were statistically significant ($p<0.05$) were included in the multivariate model. The best reduced model based on a 2 log likelihood value was built.

## RESULTS

*Analysis of Anemia Prevalence and Factors Associated with Anemia*

Of the 8886 patients who had ever attended YRG CARE and were greater than 18 years of age, 7069 had a hemoglobin value recorded in the database and were included in the analysis. 1817 patients (20.4%) did not have a hemoglobin value and were excluded from all analyses. Male-female ratio and mean age did not vary significantly between the included and excluded groups: mean age was 32 in the included group vs. 31 in the excluded group, while the included group was 69% male and the excluded group was 65% male. However, median time of follow up did vary between the two groups, with the included group having a median of 332 days of follow up, while the excluded group had a median of less than one day of follow-up.

The mean hemoglobin value for the cohort was 11.4 g/dL (SD: 2.4). Sixty percent of patients in the cohort did not have anemia, while 19% had grade 1 anemia, 13% had grade 2 anemia, 5% had grade 3 anemia, and 3% had grade 4 anemia. For the 209 patients on HAART in this cohort, the median time from HAART initiation to the date of the hemoglobin value was 12 months (IQR: 4-24 months). For the 180 patients on mono/dual therapy, the median time from therapy initiation to the date of the hemoglobin value was 13 months (IQR: 5-32 months).

Of the 7069 patients with recorded hemoglobin values, 5638 patients (79.8%) had associated CD4 cell count values. Patients with CD4 cell counts greater than 500 cell/μL

(n=1130) had a mean hemoglobin value of 12.5 g/dL (SD: 2.11); those between 351-500 cells/μL (n=742) had a mean hemoglobin of 12.5 g/dL (SD: 2.23); those between 201-350 cells/μL (n=1208) had a mean hemoglobin of 11.9 g/dL (SD: 2.32); those between 101-200 cells/μL (n=1058) had a mean hemoglobin of 11.1 g/dL (SD: 2.32); and those between 0-100 cells/μL (n=1500) had a mean hemoglobin of 10.2 g/dL (SD: 2.33). The decline in mean hemoglobin values with decreased CD4 cell count strata was statistically significant ($p<0.001$). The mean hemoglobin value for the 1431 individuals for whom a CD4 cell count was not available was 11.1 g/dL (SD 2.43). The percent of individuals without anemia declined from 78% at CD4 cell counts greater than 500 cells/μL to 40% at CD4 cell counts less than 100 cells/μL (Figure 1). Each grade of anemia had a corresponding statistically significant increasing trend with decreasing CD4 cell count strata (Figure 1).

In the case-control comparison of non-anemic and anemic individuals, univariate analysis showed that multiple factors were significantly associated with anemia (Table 1). The following factors had the strongest association: being underweight (5.4 times increased risk compared to overweight patients), having a CD4 cell count less than 100 cells/μL (5.3 times increased risk compared to those with a CD4 cell count greater than 500 cells/μL), ascites, pulmonary TB, and extrapulmonary TB. Other HIV related co-morbidities also had significant associations, including cytomegalovirus retinitis, oral candidiasis, PCP, and cryptococcal meningitis. Lack of HAART use and lack of cotrimoxazole use were both associated with a 1.4 times increased odds of anemia.

In the multivariate model, CD4 cell count less than 100 cells/μL and underweight BMI had the strongest association with anemia, though the odds ratios were reduced from the univariate results to 3.8 and 3.6 respectively (Table 1). In contrast, the odds ratio for female gender increased from 1.6 to 3.3 times increased odds of anemia in comparison to males. Pulmonary TB and extrapulmonary TB were both associated with an approximately two times increased odds of anemia, while oral candidiasis had a milder association with anemia. Lack of cotrimoxazole prophylaxis use was associated with a 1.5 times increased odds of anemia.

*Analysis of the Impact of HAART on Anemia*

After restricting the sample to those who had used HAART and had hemoglobin values recorded, 401 patients had all the data necessary to analyze the impact of HAART on anemia. In the control group, 77 patients the relevant hemoglobin values and a diagnosis of clinical or immunological AIDS but never received HAART. The median baseline CD4 counts were 163 and 218 cells/μL for HAART and control groups respectively. The mean times to follow-up hemoglobin were 7.0 and 7.1 months for the HAART and control groups respectively. Among patients who initiated HAART, the numbers on d4T vs. AZT-containing regimens were 308 and 93 patients respectively.

For patients who initiated HAART, the mean baseline hemoglobin of 10.7g/dL significantly increased to 12.4g/dL during the year of follow-up ($p<0.001$, Figure 2 and Table 2). While 46.6% of patients were not anemic at HAART initiation, this increased significantly to 78.1% during follow-up ($p<0.001$). Grades 3 and 4 anemia decreased

from 12.5% to 2% for those on HAART ($p<0.001$, Table 2). By contrast, for the control group of patients who never received HAART, the increase in mean baseline hemoglobin from 10.50 to 11.10g/dL did not reach significance ($p=0.06$, Figure 2 and Table 3). While the percent of non-anemic patients increased from 40.3 to 54.5% on follow-up in this group, this was not significant ($p=0.291$, Table 3).

**DISCUSSION**

This study highlights a high (40%) prevalence of anemia (using the WHO definition) among HIV-infected individuals in South India. Using an alternative definition of anemia (hemoglobin <12 g/dL for females and <13 g/dL for males), the prevalence of anemia is 68%, which is similar to the 70-90% prevalence reported in other developing countries.(6, 11, 15, 16) Most developing country studies have focused specifically on groups at higher risk for anemia, such as pregnant or TB co-infected patients. Since this study has patients of both genders distributed across all CD4 count strata, it may more accurately reflect the prevalence of anemia in the general HIV-infected population.

Comparison of our data with the largest available population-based data on anemia in South India (only available for women) makes clearer the increased risk of anemia in the HIV-infected population (Table 4). When applying the same definition of anemia used in population based surveys, approximately 70% of female patients at YRG CARE were anemic, compared to 50% and 57% of women in surveys from Andhra Pradesh and Tamil Nadu respectively,(2) the two Indian states from which our clinic derives its patient population. Moreover, this higher prevalence of anemia exists despite female patients at YRG CARE having a similar mean BMI and a lower percentage of underweight individuals compared to the general population, suggesting this effect is due to the impact of HIV disease rather than nutritional status alone.

The trend of increasing anemia with HIV disease progression shown in Figure 1 supports data from prior studies.(3-5) Of note, the influence of HIV disease progression starts

well before immunological AIDS, with a significant increase in the percent of patients with anemia evident even at CD4 cell counts of 201-350 cells/μL. It is important to clarify that the trends in Figure 1 do not imply that anemia increases in HIV-infected patients solely due to a decline in CD4 cell count. Rather, the trend of increasing anemia with immunosuppression likely has multiple causes, including an increased burden of opportunistic infections, higher HIV viral load, and malnutrition resulting from AIDS.

The multivariate analysis helps sort out the independent contribution of these various factors to anemia. Similar to findings in other studies,(4, 7, 13) a low CD4 cell count had a strong independent association with anemia even after controlling for major opportunistic infections and malnutrition. Unlike previous studies, however, our data shows that this increased risk happens even at CD4 cell counts greater than 200 cells/μL. This independent association between progressive immunosuppression and increasing anemia may be explained by increasing HIV viral loads that cause immunosuppression. While the exact pathophysiology of anemia due to the HIV virus itself is unclear, most studies suggest that the virus inhibits hematopoiesis either directly through infection of progenitor cells or indirectly through upregulation of cytokines.(11) Unfortunately, the prohibitive cost of viral load testing in the setting of this study precludes a direct analysis of this hypothesis. Part of the association between CD4 cell count and anemia in this study may also be due to the fact that anemia has been shown to independently accelerate immunological disease progression.(6) Alternatively, low CD4 cell count could be a surrogate marker for some other aspect of disease progression not captured in this analysis.

While the association of anemia with underweight BMI is not surprising, it is of specific relevance to the Indian setting, where the rate of chronic malnutrition is among the highest in the world, with a prevalence of childhood under-nutrition nearly double that in sub-Saharan Africa.(27) Of note, even individuals with a BMI in the normal range had twice the odds of anemia as compared to those with overweight BMIs. Low BMI is associated with deficiencies of many nutrients—including iron, folate, B12, and vitamin A—that contribute directly to anemia. The association between low BMI and anemia may also reflect widespread intestinal helminth infection, which can cause chronic blood loss and worsen micronutrient deficiencies. In addition, for particular segments of the population (e.g. upper castes with dietary restrictions), a strict vegetarian diet may exacerbate these nutrient deficiencies. The 1.3 times adjusted odds of anemia with oral candida infection may also reflect micronutrient deficiency as candidiasis, especially with esophageal involvement, can decrease oral intake.

Women had a 3.3 times adjusted odds of being anemic compared to men. This most likely reflects the high rate of baseline iron deficiency anemia in Indian women due to menstrual blood loss in the context of poor nutritional status;(2) moreover, malnutrition in India disproportionately affects females.(27) In addition, prior studies have found multiparity to be the most significant risk factor for anemia in women. Lack of cotrimoxazole prophylaxis use was associated with a 1.5 times adjusted odds of anemia, a finding previously noted in other studies.(4) While this association may seem counterintuitive, since anemia is occasionally an adverse effect of cotrimoxazole, it may

be explained by the protective effect of cotrimoxazole prophylaxis against multiple opportunistic infections which may cause anemia.

An important finding in this analysis not previously highlighted in U.S. and European studies is the two times increased odds of anemia in patients with pulmonary and extrapulmonary TB, even after adjusting for CD4 cell count and malnutrition. TB is the second most common opportunistic infection in South India after oral candidiasis (18, 28) and therefore may substantially increase the burden of anemia among HIV-infected patients in South India. Table 5 shows that the high 81% prevalence of anemia among patients with pulmonary TB in this cohort (as compared to the lower 68% prevalence using the same criteria for the overall cohort) is comparable to the prevalence found in other studies of HIV/TB co-infected patients from Malawi and Uganda.(15, 16) The etiology of anemia in TB is likely multifactorial, deriving partially from anemia of chronic disease (associated with increased IL-6) and partly from deficiencies of nutrients such as iron, vitamin A, and selenium.(15) Also, in some cases, severe anemia may be the only clue to diagnosing occult tuberculous infection of the bone marrow.(19)

It is important to highlight the way the synergistic cycle of immunosuppression, malnutrition, and TB may impact rates of anemia. High HIV viral burden and TB both cause a net catabolic state, which can lead to severe wasting.(29) Malnutrition and HIV immunosuppression are two of the strongest risk factors for TB infection.(30) TB and malnutrition have both been shown to independently accelerate immunological disease progression in HIV-infected patients.(31, 32) The net result is a downward spiral placing

HIV-infected patients in TB-endemic countries at very high risk for developing anemia. Anemia, in turn, independently accelerates the rate of immunological disease progression and decreases survival time for people living with HIV.(4, 6) Therefore, in addition to roll-out of HAART, nutritional support and aggressive diagnosis and treatment of tuberculosis should be the cornerstones of anemia management for HIV-infected individuals in India.

While Western studies have showed decreased anemia with HAART use,(14, 21, 22) to our knowledge, the study described here is the first from a developing country to examine this issue. Despite multiple co-morbidities in our patient population, our analysis suggests that the beneficial effects of HAART induced immune reconstitution on anemia are similar or even superior to those found in Western studies. *Anemia resolved in nearly 60% of patients in this sample within the first year of HAART use.* While there was also a mild increase in mean hemoglobin in the control group, this change did not reach statistical significance, and the magnitude of the change was much smaller than that in the group on HAART. This increase in mean hemoglobin in the control group may be explained by the fact that many of these patients were probably treated for opportunistic infections (especially TB), given nutritional supplementation, and started on cotrimoxazole prophylaxis prior to their follow-up hemoglobin tests. The much greater increase in mean hemoglobin in the group on HAART suggests that antiretroviral therapy adds significant benefit beyond that provided by basic clinical care without HAART, by essentially reversing the trend of increasing anemia with progressive immunosuppression (Figure 1).

The main limitation of the analysis of factors associated with anemia is its cross-sectional design, which precludes definite determination of the temporal and causal relationships between anemia and significantly associated factors. Also, the YRG CARE observation database does not capture data on laboratory findings that could better characterize the causes of anemia (i.e., mean corpuscular volume, iron studies, reticulocyte count). Therefore, it is not possible to clarify the frequency of clinically diagnosed iron deficiency, B12 deficiency, folate deficiency, or anemia of chronic disease in this population. Certain medications commonly used in this population—most importantly anti-tuberculosis therapy, but also fluconazole and ganciclovir—also could not be included the analysis because they are not captured in the database.

Many HIV-associated co-morbidities, such as PCP, cryptococcal meningitis, cytomegalovirus retinitis, oral hairy leukoplakia, lymphadenopathy, and ascites did not have statistical power to be included in the multivariate model, despite significant univariate associations. While more data would be needed to calculate their independent odds ratios, it is possible that much of the association between anemia and these factors in univariate analysis is actually due to low CD4 cell counts. For instance, 92% of PCP episodes included in this analysis, 95% of cryptococcal meningitis episodes, 97% of cytomegalovirus episodes, 83% of oral hairy leukoplakia episodes, and 93% of ascites episodes occurred at CD4 counts less than 350 cells/μL. In contrast, lymphadenopathy episodes were more widely distributed over all CD4 strata, with only 73% of cases occurring at CD4 cell counts below 350 cells/μL and 49% below 200 cells/μL.

Approximately 20% of the 8886 adult patients who had ever attended YRG CARE did not have hemoglobin values recorded in the database, which may introduce some selection bias into the study with possible over- or underestimation of the prevalence of anemia in this cohort. Many of these patients likely had absent hemoglobin values because they only visited the clinic once (as indicated by the median follow-up time of less than one day for the group) and did not return for a follow-up visit. Since YRG CARE was once the only major HIV treatment center in South India, patients frequently traveled from as far away as northern Andhra Pradesh to access care at the clinic. However, due to distance, many of these patients could not afford or were not willing to return after the initial HIV diagnosis for a follow-up visit, which is normally when baseline labs are collected. While there is no reason to believe that these patients would have had lower or higher hemoglobin values compared to the rest of the cohort (due to the similarity in demographics), we can only speculate on this point.

The analysis of the impact of HAART on anemia also has limitations. Most significantly, despite the fact that nearly 1,600 patients at YRG CARE had been started on HAART at the time this study was done, only 401 patients could be included in the analysis. This is because only 659 of the 1,600 patients on HAART had baseline hemoglobins, only 551 of these 659 patients had continued HAART for three months without significant treatment interruption, and only 401 of these 551 patients had follow-up hemoglobin values.

We do not believe that the exclusion of these patients significantly biases our study. Patients excluded due to inadequate length of HAART treatment or significant treatment interruption are not relevant to this analysis, since they would not allow us to adequately assess the impact of sustained HAART use on anemia. Patients excluded due to absence of baseline hemoglobin values likely represent individuals who either had a prior hemoglobin recorded more than three months prior to HAART initiation or who started on HAART before baseline hemoglobin testing became the standard-of-care at the clinic. Although this is a weakness of the analysis, we have no reason to believe that the demographics of these individuals would differ significantly from those included in the analysis.

## CONCLUSIONS

This study has important implication for both public health policy and the clinical management of people living with HIV/AIDS in India. Most importantly, the dramatic resolution of anemia in a large proportion of patients following HAART initiation highlights yet another way that this therapy benefits the lives of people living with HIV in developing countries. Only a few years ago, many Western public health experts doubted that distribution of HAART could be successfully implemented in the Indian context.(33) Our data contribute to a growing body of literature underscoring the positive effects of HAART roll-out in resource-limited settings, which include remarkable decreases in mortality,(34, 35) as well as in the incidence of TB and other opportunistic infections.(34, 36, 37) By reducing symptoms of fatigue and exhaustion, the resolution of anemia in many patients on HAART may drastically improve quality of life (8, 9) and increase survival time (4). In addition, it may facilitate the livelihood of people living with HIV in settings where many rely on physical labor for survival and do not have access to disability insurance. Indeed, our data should reinforce the determination for increased roll-out of HAART in developing countries, especially when this life-saving therapy still remains unavailable to the majority of those in need.(38)

This study also highlights the striking impact of undernourishment on anemia in this population, in which the synergy of tuberculosis, increased catabolism from HIV, chronic diarrhea, and esophageal candidiasis results in profound wasting. In addition to targeted nutritional supplementation (i.e., iron and B12 supplementation), programs that ensure food security for this vulnerable population may be critical to reducing the burden of

anemia. For example, one of the largest antiretroviral roll-out programs in Haiti provides its most undernourished patients with a monthly supply of beans, rice, and vegetable oil.(35) Tuberculosis also emerges as a major factor contributing to anemia, which emphasizes the importance of tuberculosis control in this population. Indeed, roll-out of HAART, nutritional support, and aggressive diagnosis and treatment of tuberculosis should be the cornerstones of anemia management for HIV-infected individuals in India. Not only are HIV-positive women three times more likely to be anemic than HIV-positive men, but they also have significantly increased risk compared to women in the general Indian population (Table 4). HIV clinicians should monitor for anemia from the moment women enroll into care, and they should be aggressive in ensuring nutritional supplementation.

The high (45-60%) prevalence of anemia in patients with CD4 cell counts less than 200 cells/μL has implications for the choice of initial HAART regimen in developing countries. Since myelosuppression is one of the adverse effects of zidovudine (AZT), use of this drug is contraindicated in patients with hemoglobins less than 11 g/dL, especially since pre-existing anemia is a risk factor for this adverse effect.(39, 40) Therefore, more than half of the patients with immunological AIDS in this cohort would not be eligible for initiation on an AZT-based HAART regimen. However, stavudine (d4T)—the only other affordable nucleoside reverse transcriptase inhibitor (NRTI) option in most resource-limited settings—may not be tolerated by many patients due to its frequent mitochondrial toxicity, which causes complications such as peripheral neuropathy, lipoatrophy, hypercholesterolemia, hyperglycemia, lactic acidosis, and pancreatitis.(41)

One approach for minimizing the toxicities of these two drugs would be to initiate patients on a d4T-containing regimen and then substitute AZT for d4T 6-12 months after initiation. Since our data shows that HAART use contributes to resolution of anemia in approximately 60% of patients within one year of therapy initiation, a majority of patients started on d4T-containing HAART would eventually become non-anemic and qualify for AZT substitution. AZT substitution would then prevent the long-term toxicities of d4T. While most patients started on d4T-containing regimens could benefit from AZT-substitution, a significant subset of patients may have persisting anemia despite long-term HAART use. When such patients experience toxicity severe enough to require d4T discontinuation, they are often left without any affordable NRTI option for their HAART regimens. This highlights the urgent need to make NRTIs with different toxicity profiles, such as tenofovir and abacavir, more accessible in resource-limited settings.

Our data also suggest that earlier initiation of HAART may help reduce the incidence of anemia and minimize toxicities from d4T and AZT. Current WHO guidelines recommend initiating HAART in relatively asymptomatic (WHO stages I and II) patients only at CD4 counts <200 cells/μL.(25) However, our data show that the risk of anemia in HIV-infected patients begins to increase even at CD4 counts <350 cells/μL, with the majority of patients being anemic at CD4 counts <200 cells/μL (as compared to only 22% at CD4 counts >350 cells/μL). Therefore, early initiation of HAART in asymptomatic patients with CD4 counts >350 cells/μL may help prevent the development of anemia in a significant proportion of patients. Early HAART initiation would also

mean that a larger proportion of patients would qualify for an AZT-containing regimen (since a larger proportion would be non-anemic), which would help minimize usage of the relatively more toxic drug d4T. It may also greatly decrease the burden of tuberculosis in this population, since a large proportion of HIV-infected individuals in TB-endemic settings experience episodes of active tuberculosis even at CD4 counts between 200-350 cells/μL.(42) While earlier therapy initiation may increase the overall cost of HAART use in developing countries, by preventing the development of anemia, this approach may actually bring significant economic benefits by allowing people living with HIV to lead more active and productive lives.(8-10)

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## FIGURES, TABLES, AND ILLUSTRATIONS

**Figure 1: Percent of Patients with Different Grades of Anemia at Various CD4 cell count strata**

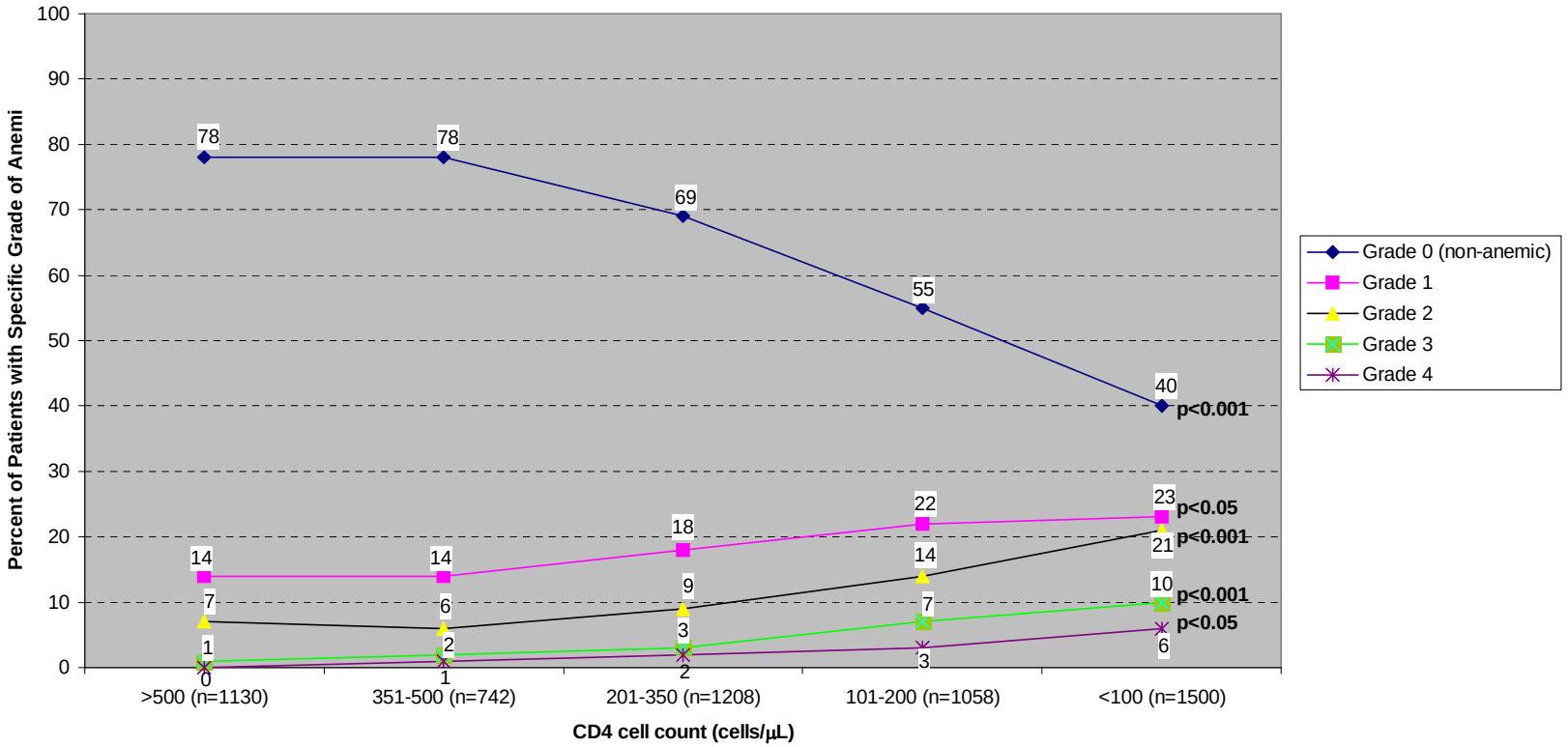

**Figure 2: Change in Hemoglobin after initiation of HAART**

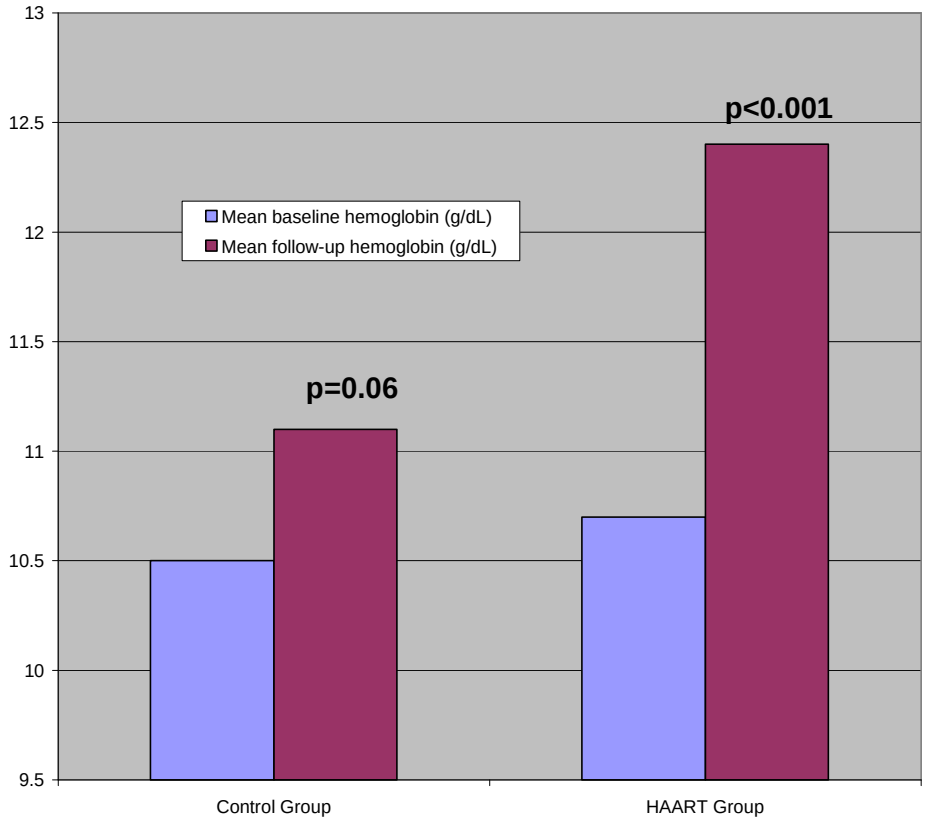

**Figure 3: Change in the Percent of People with Anemia after Initiation of HAART**

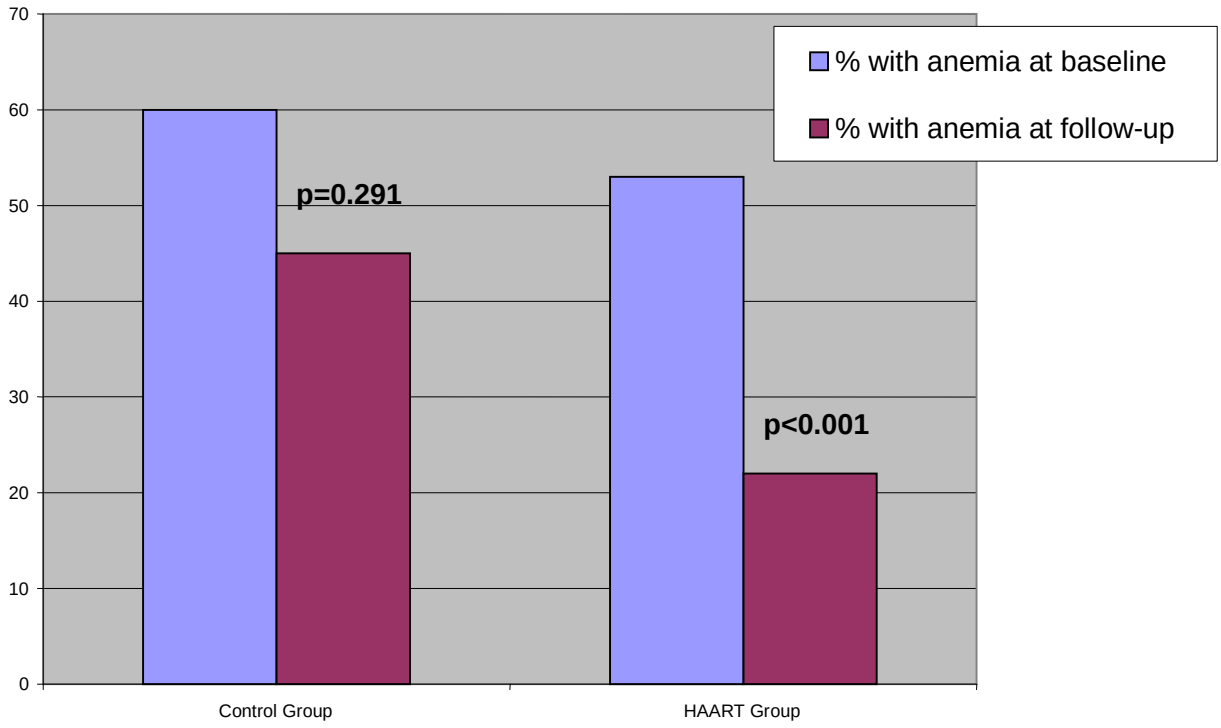

**Table 1: Factors Associated with Anemia in the Univariate and Multivariate Analyses**

| *Risk factor* | *Non-anemic N (%)* | *Anemic N (%)* | *Univariate Odds Ratio (CI)* | *Multivariate Odds Ratio (CI)* |
|---|---|---|---|---|
| **Gender** | | | | |
| Male | 3136 (74) | 1771 (63) | 1.0 | 1.0 |
| Female | 1129 (26) | 1030 (37) | 1.6 (1.5-1.8) | 3.3 (2.9-3.7) |
| **Age** | | | | |
| 18-30 | 1842 (43) | 1101 (39) | 1.0 | 1.0 |
| 31-50 | 2261 (53) | 1572 (56) | 1.2 (1.05-1.3) | 1.1 (1.01-1.3) |
| >50 | 163 (4) | 130 (5) | 1.3 (1.04-1.7) | 1.6 (1.2-2.04) |
| **Body Mass Index** | | | | |
| Overweight (>25) | 373 (9) | 67 (2) | 1.0 | 1.0 |
| Normal (18.5-24.9) | 1499 (35) | 641 (23) | 2.4 (1.8-3.1) | 1.9 (1.5-2.6) |
| Underweight (<18.5) | 897 (21) | 872 (31) | 5.4 (4.1-7.1) | 3.6 (2.6-4.8) |
| Not available | 1497 (35) | 1223 (44) | -- | |
| **CD4 cell count (cells/μL)** | | | | |
| >500 | 882 (21) | 248 (9) | 1.0 | 1.0 |
| 351-500 | 578 (13) | 164 (6) | 1.0 (0.8-1.3) | 0.94 (0.7-1.2) |
| 201-350 | 833 (19) | 375 (13) | 1.6 (1.3-1.9) | 1.4 (1.2-1.8) |
| 101-200 | 579 (14) | 479 (17) | 2.9 (2.4-3.5) | 2.2 (1.8-2.7) |
| 0-100 | 599 (14) | 901 (32) | 5.3 (4.5-6.4) | 3.8 (3.1-4.6) |
| Not available | 795 (19) | 636 (23) | -- | |
| **ART use** | | | | |
| On HAART | 140 (3) | 69 (3) | 1.0 | |
| On Mono or dual therapy | 112 (3) | 68 (2) | 1.2 (0.8-1.8) | |
| Not on ART | 4014 (94) | 2666 (95) | 1.4 (1.01-1.8) | |
| **Use of Cotrimoxazole Prophylaxis** | | | | |
| Yes | 273 (6) | 134 (5) | 1.0 | 1.0 |
| No | 3993 (94) | 2669 (95) | 1.4 (1.1-1.7) | 1.5 (1.2-2.0) |
| **Pulmonary tuberculosis** | | | | |
| No | 2690 (63) | 1155 (41) | 1.0 | 1.0 |
| Yes | 1576 (37) | 1648 (59) | 2.5 (2.2-2.7) | 1.9 (1.6-2.1) |
| **Extrapulmonary TB** | | | | |
| No | 3898 (91) | 2261 (81) | 1.0 | 1.0 |
| Yes | 368 (9) | 542 (19) | 2.5 (2.2-2.9) | 2.1 (1.8-2.4) |
| **Oral Candidiasis** | | | | |
| No | 2642 (62) | 1219 (43) | 1.0 | 1.0 |
| Yes | 1624 (38) | 1584 (57) | 2.1 (1.9-2.3) | 1.3 (1.1-1.4) |
| **Esophageal Candidiasis** | | | | |
| No | 4179 (98) | 2700 (96) | 1.0 | |
| Yes | 87 (2) | 103 (4) | 1.8 (1.4-2.4) | |
| **PCP** | | | | |
| No | 4063 (95) | 2539 (91) | 1.0 | |
| Yes | 203 (5) | 264 (9) | 2.1 (1.7-2.5) | |
| **Cryptococcal meningitis** | | | | |
| No | 4188 (98) | 2704 (96) | 1.0 | |

| | | | | |
|---|---|---|---|---|
| Yes | 78 (2) | 99 (4) | 2.0 (1.5-2.6) | |
| **CMV** | | | | |
| No | 4228 (99) | 2745 (98) | 1.0 | |
| Yes | 38 (1) | 58 (2) | 2.4 (1.6-3.6) | |
| **Oral hairy leukoplakia** | | | | |
| No | 4063 (95) | 2639 (94) | 1.0 | |
| Yes | 203 (5) | 164 (6) | 1.2 (1.01-1.5) | |
| **Lymphadenopathy** | | | | |
| No | 3693 (87) | 2264 (81) | 1.0 | |
| Yes | 573 (13) | 539 (19) | 1.5 (1.3-1.7) | |
| **Herpes zoster** | | | | |
| No | 3561 (84) | 2355 (84) | 1.0 | |
| Yes | 705 (16) | 448 (16) | 0.96 (0.84-1.1) | |
| **Herpes simplex** | | | | |
| No | 3774 (89) | 2452 (88) | 1.0 | |
| Yes | 492 (11) | 351 (12) | 1.1 (0.9-1.3) | |
| **Gastroenteropathy** | | | | |
| No | 3807 (89) | 2405 (86) | 1.0 | 1.0 |
| Yes | 459 (11) | 398 (14) | 1.4 (1.2-1.6) | 1.1 (0.4-1.3) |
| **Bacterial infections of the skin** | | | | |
| No | 4206 (99) | 2767 (99) | 1.0 | |
| Yes | 60 (1) | 36 (1) | 0.9 (0.6-1.4) | |
| **Ascites** | | | | |
| No | 4256 (100) | 2780 (99) | 1.0 | |
| Yes | 10 (0) | 23 (1) | 3.5 (1.7-7.4) | |
| **Renal Disease** | | | | |
| No | 4148 (97) | 2717 (97) | 1.0 | |
| Yes | 118 (3) | 86 (3) | 1.1 (0.7-1.2) | |
| **Syphilis** | | | | |
| No | 2504 (59) | 1559 (56) | 1.0 | |
| Yes | 184 (4) | 125 (4) | 1.1 (0.9-1.4) | |
| Not tested | 1578 (37) | 1119 (40) | -- | |
| **Malaria** | | | | |
| No | 4240 (99) | 2780 (99) | 1.0 | |
| Yes | 24 (1) | 23 (1) | 1.5 (0.8-2.6) | |

**Table 2: Impact of at least three months of HAART use on the severity of anemia and hemoglobin values during the first year after HAART initiation (n=401)**

| | **At HAART initiation** (number of patients (%)) | **At time of follow-up** (number of patients (%)) | **p-value** |
|---|---|---|---|
| **No anemia** | 187 (46.6) | 313 (78.1) | |
| **Grade 1** | 92 (22.9) | 59 (14.7) | |
| **Grade 2** | 72 (18.0) | 21 (5.2) | |
| **Grade 3** | 30 (7.5) | 6 (1.5) | |
| **Grade 4** | 20 (5.0) | 2 (0.5) | <0.001 |
| **Mean Hemoglobin** (g/dL) | 10.65 | 12.35 | <0.001 |

**Table 3: Change in severity of anemia and hemoglobin values during the first year for patients who qualified for HAART (i.e. clinical or immunological AIDS) but never initiated therapy (n=77)**

| | **At time of AIDS diagnosis** (number (%)) | **At time of follow-up** (number (%)) | **p-value** |
|---|---|---|---|
| **Grade 0** | 31 (40.3) | 42 (54.5) | |
| **Grade 1** | 23 (29.9) | 14 (18.2) | |
| **Grade 2** | 16 (20.8) | 11 (14.3) | |
| **Grade 3** | 6 (7.8) | 10 (13.0) | |
| **Grade 4** | 1 (1.3) | 0 (0.0) | 0.291 |
| **Mean Hemoglobin** (g/dL) | 10.50 | 11.10 | 0.06 |

**Table 4: Prevalence of anemia among women at YRG CARE versus women in the general population of South India**(2)

| **Severity of Anemia*** | **YRG CARE (n=2159)** | **Tamil Nadu state (n=5456)** | **Andra Pradesh state (n=7216)** |
|---|---|---|---|
| Any anemia (%) | 70.4 | 56.5 | 49.8 |
| Mild (%) | 41.5 | 36.7 | 32.5 |
| Moderate (%) | 25.4 | 15.9 | 14.9 |
| Severe (%) | 3.5 | 3.9 | 2.4 |
| Mean body mass index ($kg/m^2$) | 20.3 | 21.0 | 20.3 |
| BMI <18.5 (%) | 24.5 | 29.0 | 37.4 |

*Based on the following definitions: "Any anemia" is any hemoglobin value <12 g/dL, "mild anemia" is any hemoglobin value between 10.0-11.9 g/dL, "moderate anemia" is any hemoglobin value between 7.0-9.9 g/dL, and "severe anemia" is any hemoglobin value <7 g/dL.

**Table 5: Prevalence of Anemia in HIV and Pulmonary TB Co-infected Patients in Various Studies from Developing Countries**

| Study Location | Total N in cohort (HIV+/HIV-) | Prevalence of Anemia in HIV/TB co-infected Patients* | Prevalence of Anemia in TB-infected but HIV-negative Patients | Mean BMI of HIV/TB co-infected Patients |
|---|---|---|---|---|
| YRG CARE, South India | 3224/0 | 81% | --- | 18.8 |
| Malawi(15) | 370/130 | 88% | 77% | 18.4 |
| Uganda(16) | 261/278 | 71% | 50% | 18.5 |

*All three prevalences of anemia above use a definition of anemia as any hemoglobin <12 g/dL in women and <13 g/dL in men

**Illustration 1**


Front of YRG CARE clinic at night.

**Illustration 3**

The staff of YRG CARE with actor Richard Gere.