Published in final edited form as:

J Acquir Immune Defic Syndr. 2011 August 15; 57(5): e101–e105. doi:10.1097/QAI.0b013e31821d3507.

Predictors of CD4 Eligibility for Antiretroviral Therapy Initiation Among HIV-Infected Pregnant Women in Lusaka, Zambia

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Abstract

In resource-limited settings, CD4 testing is a barrier to antiretroviral therapy initiation in pregnancy. We used logistic regression to identify predictors of CD4+ cell count ≤ 350 cells/uL in 20,233 pregnant women. The best-performing model included any 3 of: age ≥ 28 years old, hemoglobin ≤ 9.8 g/dL, gestational age ≤ 30 weeks, weight ≤ 64 kg, history of tuberculosis or previous death of an infant prior to one year old. Sensitivity was 45.7% (95% CI: 44.5-47.0), specificity 70.7% (95% CI: 69.6-71.8), and misclassification rate 41.4% (95% CI: 40.5-42.2). CD4 triage remains a critical element of maternal HIV care and PMTCT.

Keywords

HIV; pregnancy; CD4; predictor; PMTCT; antiretroviral therapy eligibility

Introduction

Despite known interventions to prevent mother to child transmission of HIV (PMTCT), an estimated 430,000 children worldwide became newly infected with HIV in 2008.¹ Combination antiretroviral therapy (ART) commenced during pregnancy dramatically reduces vertical transmission.²⁻⁴ However, because of heavy disease burdens and overstretched healthcare systems, availability of such interventions are limited in most resource-constrained settings. Global criteria to start ART in pregnancy, though, are expanding. In 2009, the World Health Organization (WHO) recommended that pregnant women with a CD4+ cell count ≤ 350 cells/uL start ART⁵ since they represent the majority of women who transmit HIV to their infants and in whom maternal and infant morbidity and mortality occur.⁶⁻¹⁰ Since 2008, Zambia has used this CD4 criteria for ART eligibility in pregnancy.¹¹

Access to CD4 testing in many parts of the world remains a formidable challenge. In 2008, WHO estimated that only 12% of HIV-infected pregnant women were assessed for ART

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The abstract of this article was presented as a poster at the International AIDS Conference; July 2010; Vienna, Austria. The data have not been previously published.

The authors have no funding or conflicts of interest to disclose.

eligibility through clinical staging or CD4 screening.¹² Even when the test is purportedly available, results can take weeks - even months - to return,¹³ which may shorten the interval between initiation of ART and delivery. Furthermore, opportunities to impact maternal health may be delayed or missed. Algorithms that predict the likelihood of an HIV-infected pregnant woman having a CD4+ cell count ≤ 350 cells/uL could be an attractive alternative, especially if inexpensive and easy to implement. In this report we evaluate maternal predictors of CD4+ cell count ≤ 350 cells/uL.

Methods

In Zambia, PMTCT services have been offered routinely during antenatal care since 2002 and have been described elsewhere.¹⁴ Opt-out HIV testing is practiced nationwide. Point-of-care hemoglobin and syphilis screening are standard, as is reflex CD4 testing. WHO clinical staging in pregnancy generally occurs after CD4 testing. In Lusaka, a city of 2 million people, twenty-five public sector sites use the Zambia Electronic Perinatal Record System (ZEPRS), a networked patient-level electronic medical record system which captures information regarding antenatal care and PMTCT.

We conducted a retrospective study of all HIV-infected women enrolling into antenatal care in government clinics in Lusaka from 1 May 2007 to 30 June 2009 through ZEPRS. We included only women newly diagnosed with HIV, thus removing potential biases that might arise from those already on ART. We excluded details of repeat pregnancies, defined as subsequent pregnancies entered into ZEPRS for one mother. We examined factors that could potentially predict CD4+ cell count ≤ 350 cells/uL in pregnancy. Maternal demographic, historical, and clinical data are routinely captured at the first antenatal visit. History of stillbirth and preterm birth were ascertained by self-report. Gestational age was estimated by last menstrual period and corroborated or changed according to abdominal palpation of uterine size.

Using multivariate logistic regression, we calculated the adjusted odds ratios (AORs) with corresponding 95% confidence intervals for the associations between each potential factor and CD4+ cell count ≤ 350 cells/uL. To ensure the practicality of such a model in the clinical setting, we restricted the potential factors to all categorical variables with at least a 33% increase or decrease in odds and all continuous variables. The misclassification rate, calculated as the sum of the false positive rate and the false negative rate, was used as an overall measure of the discriminatory abilities of the predictive models.

We calculated the misclassification rate for all possible combinations of the selected factors. For combinations with continuous variables, we iteratively dichotomized the patients across a wide range of values and calculated separate misclassification rates. We defined the best-performing predictor for CD4+ cell count ≤ 350 cells/uL as the model which minimized the misclassification rate. We evaluated each model for sensitivity, specificity, positive predictive value, and negative predictive value.

Analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC) and R software version 2.4.1 (<http://www.r-project.org>). Use of these routinely collected clinical data was approved by the ethical review committees at the University of Zambia (Lusaka, Zambia) and University of Alabama at Birmingham (Birmingham, Alabama, USA).

Results

Between 1 May 2007 and 30 June 2009, 138,884 pregnancies were registered in ZEPRS. For 823 women with multiple recorded pregnancies, only data from the first pregnancy were included. Of the 133,238 (95.9%) women who had an HIV test, 28,976 (21.7%) tested HIV

positive. The 3,018 (10.4%) women who knew their positive HIV status before were excluded from the analysis.

20,233 (77.9%) of the 25,958 newly-diagnosed HIV-infected pregnant women had a documented CD4 result; of these 9,876 (48.8%) women had a CD4+ cell count $\leq$ 350 cells/uL. Compared to women without a CD4 result available, women with CD4 results were younger (median age of 26 years vs. 27 years; $p < 0.01$), had a lower median hemoglobin measurement (11.1 g/dl vs. 11.6 g/dl; $p < 0.01$), had lower levels of education (40.5% with primary education vs. 36.2%; $p < 0.01$), had higher rates of syphilis (22.2% versus 18.6%; $p < 0.01$), and were less likely to have a reported history of tuberculosis (TB) (2.8% versus 3.7%; $p < 0.01$) and a previous death on an infant prior to one year old (5.4% versus 7.0%; $p < 0.01$). There were no differences with regard to gestational age at first antenatal visit, weight, malaria during the current pregnancy, marital status, parity, and previous child death prior to five years old (data not shown).

Predictors of CD4+ cell count $\leq$ 350 cells/uL in pregnancy

In multivariable analysis [Table 1], the following categorical variables were significantly associated with CD4+ cell count $\leq$ 350 cells/uL: history of TB (AOR: 1.48, 95% CI: 1.20-1.84) and previous death of an infant prior to one year old (AOR: 1.58, 95% CI: 1.36-1.82). Additional associated factors included primary/no education (AOR: 0.86, 95% CI: 0.80-0.92), parity > 2 (AOR: 0.88, 95% CI: 0.80-0.96), and previous child death prior to five years old (AOR: 1.31, 95% CI: 1.15-1.50). Continuous variables included in the analysis were age at first antenatal visit (years), baseline hemoglobin (g/dL), gestational age at first antenatal visit (weeks) and baseline weight (kg). The best performing predictive models based upon a single variable are listed in Table 2.

We then constructed predictive models based upon combinations of variables [Table 2]. A model that utilized only self-reported characteristics (age, history of TB, and previous death of an infant prior to one year old) had a misclassification rate of 43.8%. Overall, the best performing model to predict CD4+ cell count $\leq$ 350 cells/uL in pregnancy was based upon at least three of the following: age $\geq$ 28 years old, hemoglobin $\leq$ 9.8 mg/dl, gestational age $\leq$ 30 weeks at first antenatal visit, weight $\leq$ 64 kg, history of TB or previous death of an infant prior to one year old. This model had a sensitivity of 45.7%, specificity of 70.7%, positive predictive value of 59.4%, negative predictive value of 58.2%, and misclassification rate of 41.4%. In comparison, a simple model that assumed all HIV-infected pregnant women had CD4+ cell count $\leq$ 350 cells/uL approximated this misclassification at 51.7%, with a sensitivity of 100% and specificity of 0%. According to the best performing model, 5,066 out of 13,599 pregnant women (37.3%) were classified as in need of treatment. The median CD4+ cell count of these women was significantly lower than the median CD4+ cell count of women not classified as needing treatment (306 (IQR: 192,447) vs. 392 (IQR: 269, 532); p -value < 0.01).

As a secondary analysis, we performed a multivariate logistic regression analysis using the six predictors of the best performing model (including age, hemoglobin, weight, and estimated gestational age at first antenatal visit as continuous variables) to determine predicted probabilities of having a CD4+ cell count $\leq$ 350 cells/uL. We classified a pregnant woman as having a CD4+ cell count $\leq$ 350 cells/uL if the predicted probability was greater than 50%. The misclassification rate from this model was 42.2%.

Discussion

We found that the following maternal characteristics were associated with CD4+ cell count $\leq$ 350 cells/uL: older age, low hemoglobin, earlier gestational age at first antenatal visit, low

weight, history of TB, and previous infant death. While 37.3% of the pregnant women who met criteria of our best-performing model not only were in need of ART but also had a significantly lower median CD4+ cell count, the misclassification rate was 41.4%. Thus, a validation analysis was not conducted to see if the predictive models were generalizable. The reduction by 10% in misclassification reflects a 20% relative improvement in correctly predicting that a woman with these maternal characteristics would have CD4+ cell count $\leq$ 350 cells/uL. However, overall performance of the models remained poor. Several variables, such as history of TB, were specific but had low positive predictive values given the low self-reported prevalence of TB in our population. Given that 50% of HIV-infected pregnant women are likely to qualify for ART based on a CD4+ cell count $\leq$ 350 cells/uL,^{13, 15-17} it is highly unlikely that a model will be able to eliminate misclassification dramatically.

To our knowledge, this analysis is unique because it focuses on simple predictors of low CD4+ cell count in pregnant HIV-infected women. While one study examined predictors of mortality in HIV-infected pregnant women,¹⁸ another built a predictor model for ART initiation in pregnant women based on self-reported symptoms.¹⁹ Our analysis focuses on characteristics that are demographic and historical, and thus could be easy to implement in resource-limited settings where non-trained workers sometimes provide care. We acknowledge several limitations of this analysis. This cohort comprises an urban population and may not be generalizable to rural settings.²⁰ We were also limited to factors that are already captured in antenatal care and thus did not include WHO clinical staging for HIV disease. However, other studies have shown that pregnant women often present at WHO Stage 1 or 2.^{17, 21, 22}

Implementation of the 2009 WHO PMTCT guidelines will likely result in half of all HIV-infected pregnant women becoming eligible for ART based on CD4 criteria. This percentage may increase by an additional 6%- 20% after WHO clinical staging is performed.^{9, 10, 17} Given the current situation of limited access to CD4 testing in many resource-constrained settings and the efficacy of ART in pregnancy,^{3, 23} policy makers could consider initiating ART in all HIV-infected pregnant women who do not have access to CD4+ cell counts.²⁴ However, such a policy would be costly and present issues of side effects of life-long ART and multi-drug resistance.²⁵ Another alternative is scale up of point-of-care CD4 testing²⁶ and efforts should continue to develop the technology so that it remains applicable to resource-constrained settings.

Ensuring timely initiation of ART among eligible pregnant women remains a major public health priority and addresses WHO Millennium Development Goals to reduce maternal mortality and achieve universal access to HIV treatment. Unfortunately, we demonstrate poor performance in predicting CD4+ cell count $\leq$ 350 cells/uL among HIV-infected pregnant women in Lusaka. Our analysis reveals that CD4 triage remains a critical element of maternal HIV care and PMTCT.

Acknowledgments

We would like to thank the Zambian Ministry of Health and Lusaka District Health Management Team for their continued support of operational research.

K.C.L. wrote the first draft, supported interpretation of results, and was responsible for editing the final manuscript. B.H.C., J.S.A.S., and E.M.S. conceived the study, guided the analysis, and interpreted the data. M.J.G performed the statistical analysis and heavily assisted with writing the methods section. All authors contributed to subsequent drafts and approved of the final version.

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Table 1
Crude odds ratio and adjusted odds ratio for predictors of pregnant women with CD4+ cell count ≤ 350 cells/uL, Lusaka Zambia (May 2007 – June 2009; N=20,233)

Maternal Characteristic	Proportion of Women with CD4 ≤ 350 (%)	Crude Odds Ratio	Adjusted Odds Ratio
Educational Level			
Tertiary/Secondary	4,235/8,501(49.8)	1.0	1.0
Primary/Nil	4,292/8,958(47.9)	0.93 (0.87 - 0.98)	0.86 (0.80 - 0.92)
Missing Information	1,349/2,774(48.6)	0.95 (0.88 - 1.04)	0.93 (0.83 - 1.04)
History of Preterm Delivery			
No	9,393/19,351(48.5)	1.0	1.0
Yes	483/882(54.8)	1.28 (1.12 - 1.47)	1.17 (1.00 - 1.37)
History of Stillbirth			
No	9,650/19,790(48.8)	1.0	1.0
Yes	226/443(51.0)	1.09 (0.91 - 1.32)	0.88 (0.70 - 1.10)
History of Tuberculosis			
No	8,340/17,286(48.2)	1.0	1.0
Yes	316/506(62.5)	1.78 (1.49 - 2.14)	1.48 (1.20 - 1.84)
Missing Information	1,220/2,441(50.0)	1.07 (0.98 - 1.17)	1.05 (0.88 - 1.25)
Malaria in Current Pregnancy, Reported at First Antenatal Care Visit			
No	8,280/17,078(48.5)	1.0	1.0
Yes	302/593(50.9)	1.10 (0.94 - 1.30)	1.05 (0.87 - 1.28)
Missing Information	1,294/2,562(50.5)	1.08 (1.00 - 1.18)	1.05 (0.88 - 1.25)
Marital Status			
Married/Cohabiting	8,754/17,899(48.9)	1.0	1.0
Single	674/1,427(47.2)	0.94 (0.84 - 1.04)	1.13 (1.00 - 1.30)
Divorced/Widowed	101/186(54.3)	1.24 (0.93 - 1.66)	1.12 (0.80 - 1.58)
Missing Information	347/721(48.1)	0.97 (0.84 - 1.12)	0.95 (0.78 - 1.15)
Parity			
0	1,778/4,009(44.4)	1.0	1.0
1-2	5,014/10,398(48.2)	1.03 (0.97 - 1.10)	1.04 (0.96 - 1.12)

Maternal Characteristic	Proportion of Women with CD4 $\leq$ 350 (%)	Crude Odds Ratio	Adjusted Odds Ratio
>2	3,084/5,826(52.9)	1.28 (1.19 - 1.36)	0.88 (0.80 - 0.96)
Previous Child Death Less than 1 Year Old			
No	9,189/19,132(48.0)	1.0	1.0
Yes	687/1,101(62.4)	1.80 (1.58 - 2.04)	1.58 (1.36 - 1.82)
Previous Child Death Less than 5 Years Old			
No	9,074/18,855(48.1)	1.0	1.0
Yes	802/1,378(58.2)	1.50 (1.34 - 1.68)	1.31 (1.15 - 1.50)
RPR Test Result			
Non reactive	7,948/16,154(49.2)	1.0	1.0
Reactive, untreated	240/526(45.6)	0.80 (0.64 - 1.01)	0.83 (0.64 - 1.09)
Reactive, treated	138/315(43.8)	0.87 (0.73 - 1.03)	0.87 (0.72 - 1.06)
Unknown	1,550/3,238(47.9)	0.95 (0.88 - 1.02)	0.98 (0.89 - 1.07)

Table 2
Misclassification rate for various algorithms to predict CD4+ cell count $\leq$ 350 cells/uL in pregnancy, Lusaka Zambia (May 2007 – June 2009; N=13,599*)

Models to predict pregnant women with CD4+ cell count $\leq$ 350 cells/uL	Misclassification Rate (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)	% of Women Classified as In Need of ART
Assume everyone has a CD4+ cell count $\leq$ 350 cells/uL	51.7 (50.8 - 52.5)	100.0 (99.9 - 100.0)	0.0 (0.0 - 0.1)	48.3 (47.5 - 49.2)	(-)	100.0 (100.0 - 100.0)
Assume no one has a CD4+ cell count $\leq$ 350 cells/uL	48.3 (47.5 - 49.2)	0.0 (0.0 - 0.1)	100.0 (99.9 - 100.0)	(-)	51.7 (50.8 - 52.5)	0.0 (0.0 - 0.0)
Models of one predictor						
Age $\geq$ 28 years old	44.3 (43.4 - 45.1)	45.4 (44.2 - 46.6)	65.4 (64.2 - 66.5)	55.1 (53.8 - 56.4)	56.1 (55.0 - 57.2)	39.8 (39.0 - 40.7)
Hemoglobin $\leq$ 10.4 g/dl	43.7 (42.9 - 44.6)	38.5 (37.3 - 39.7)	72.9 (71.9 - 74.0)	57.1 (55.6 - 58.6)	55.9 (54.9 - 56.9)	32.6 (31.8 - 33.4)
Gestational age $\leq$ 19 weeks at first antenatal care visit	48.0 (47.2 - 48.8)	29.7 (28.6 - 30.8)	72.9 (71.8 - 73.9)	50.6 (49.0 - 52.2)	52.5 (51.5 - 53.5)	28.4 (27.6 - 29.1)
Weight $\leq$ 53 kg	47.0 (46.2 - 47.9)	25.7 (24.7 - 26.8)	78.5 (77.6 - 79.5)	52.8 (51.1 - 54.6)	53.0 (52.1 - 54.0)	23.5 (22.8 - 24.2)
History of TB	47.7 (46.8 - 48.5)	3.6 (3.2 - 4.1)	97.9 (97.6 - 98.3)	62.2 (57.2 - 67.1)	52.1 (51.2 - 52.9)	2.8 (2.6 - 3.1)
Previous death of an infant prior to 1 year old	47.1 (46.3 - 48.0)	7.1 (6.5 - 7.8)	95.7 (95.2 - 96.1)	60.8 (57.3 - 64.3)	52.4 (51.5 - 53.3)	5.7 (5.3 - 6.1)
Models of two predictors						
Age $\geq$ 25 years old AND Hemoglobin $\leq$ 11.6 g/dl	42.8 (42.0 - 43.6)	47.1 (45.8 - 48.3)	66.7 (65.6 - 67.8)	56.9 (55.6 - 58.2)	57.4 (56.3 - 58.4)	40.0 (39.1 - 40.8)
Age $\geq$ 29 years old OR Hemoglobin $\leq$ 10.0 g/dl	42.7 (41.9 - 43.5)	56.3 (55.0 - 57.5)	58.3 (57.1 - 59.4)	55.8 (54.6 - 57.0)	58.7 (57.6 - 59.9)	48.8 (47.9 - 49.6)
Models of three predictors						
Age $\geq$ 30 years old OR Hemoglobin $\leq$ 10.0 mg/dl OR Previous death of an infant prior to 1 year old	42.4 (41.6 - 43.2)	54.8 (53.6 - 56.0)	60.3 (59.1 - 61.4)	56.3 (55.1 - 57.6)	58.7 (57.6 - 59.9)	47.0 (46.2 - 47.9)
At least 2 of: Age $\geq$ 25 years old, Hemoglobin $\leq$ 12.0 g/dl, Weight $\leq$ 68 kg	42.6 (41.7 - 43.4)	43.7 (42.5 - 44.9)	70.3 (69.2 - 71.4)	57.9 (56.6 - 59.3)	57.1 (56.1 - 58.2)	36.4 (35.6 - 37.3)
Age $\geq$ 28 years old OR History of TB OR Previous death of an infant prior to 1 year old	43.8 (42.9 - 44.6)	49.9 (48.7 - 51.1)	62.1 (61.0 - 63.3)	55.2 (54.0 - 56.5)	57.0 (55.9 - 58.1)	43.7 (42.9 - 44.5)
Models of six predictors						
At least 3 of: Age $\geq$ 28 years old, Hemoglobin $\leq$ 9.8 g/dl, Gestational age $\leq$ 30 weeks at first antenatal care visit, Weight $\leq$ 64 kg, History of TB, Previous death of an infant prior to 1 year old	41.4 (40.5 - 42.2)	45.7 (44.5 - 47.0)	70.7 (69.6 - 71.8)	59.4 (58.0 - 60.7)	58.2 (57.1 - 59.2)	37.3 (36.4 - 38.1)

* Patients with a missing value for any of the six characteristics were removed from the multivariable model