PREDICTION MODEL OF PRETREATMENT HIV RNA LEVELS IN NAÏVE HIV-INFECTED PATIENTS: APPLICATION FOR RESOURCE-LIMITED SETTING

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Abstract. A prediction model for pretreatment HIV RNA level ≤100,000 copies / ml would provide a useful tool for selection of abacavir (ABC) or rilpivirine (RPV) in the first-line regimen in a resource-limited setting. Factors associated with pretreatment HIV RNA ≤100,000 copies/ml were determined from a cohort of 1,223 patients divided into a derivation (n = 873) and the remaining in a validation group. Their median [interquartile range (IQR)] age was 36.3 (30.5-42.9) years, CD4 count 122 (39-216) cells/mm^3 and pre-treatment HIV RNA level 100,000 (32,449-229,777) copies/ml. Factors associated with pretreatment HIV RNA ≤100,000 copies/ml were non-anemia [odds ratio (OR)= 2.05; 95% confidence interval (CI): 1.28-3.27, p= 0.003], CD4 count ≥200 cells/mm^3 (OR= 3.00; 95% CI: 2.08-4.33, p<0.001) and non-heterosexual HIV exposure (OR= 1.61; 95% CI: 1.07-2.43, p= 0.021). The area under a receiver operating characteristic curve was 0.66 (95% CI: 0.62-0.69), but specificity was 97.3%. The prediction model identified a set of readily available clinical data but lacked the requisite predictive performance to fulfill its purpose.

Keywords: abacavir, HIV RNA level, prediction model, rilpivirine, Thailand

INTRODUCTION

Since the launch of Thailand National AIDS Program in 2012, antiretroviral therapy (ART) has become more accessible to Thai HIV-infected individuals, resulting in significantly decreased morbidity and mortality (Jongwutiwes *et al*, 2007; Boender *et al*, 2015). According to Thailand National Guidelines on HIV/AIDS Treatment and Prevention 2017, the recommended first-line ARTs are efavirenz (EFV), emtricitabine (FTC) or lamivudine (3TC) and tenofovir disoproxil fumarate (TDF) (Department of Disease Control, 2017). However, this regimen is still not an ideal ART regimen for all HIV-infected patients as adverse effects limit usage in

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certain groups, such as those with kidney or neuropsychiatric disease (Gupta *et al*, 2005; Cespedes and Aberg, 2006). Alternative regimens for such Thai patients are abacavir (ABC) or zidovudine (AZT) and 3TC plus either nevirapine (NVP) or rilpivirine (RPV) (Department of Disease Control, 2017).

Adverse effects of antiretroviral drugs is of important concerns to both patients and health-care providers. For instance, EFV-associated neuropsychiatric adverse effects are not uncommon, with such symptoms as abnormal dreams and dizziness, which can persist in some instances for several months to years (Vrouenraets *et al*, 2007). In addition, patients may experience symptoms of depression at any time during treatment (Mills *et al*, 2013; Mollan *et al*, 2014). RPV is an alternative non-nucleoside reverse transcriptase inhibitor (NNRTI) with non-inferior efficacy and fewer neuropsychiatric side effects than EFV (Sax *et al*, 2009; Cohen *et al* 2011; Sax *et al*, 2011). Nevertheless, use of ABC (except if in combination with dolutegravir or 3TC) and RPV in first-line regimens for treatment-naïve HIV-infected patients with pretreatment HIV RNA >100,000 copies/ml are not recommended due to high rates of treatment failure (Sax *et al*, 2009; Sax *et al*, 2011; Behrens *et al*, 2014). Thus, the levels of pretreatment HIV RNA should be measured before starting ABC or RPV in treatment-naïve HIV-infected patients.

In Thailand, measurement of pretreatment HIV RNA level is not routinely performed due to limited resources (Boender *et al*, 2015; Department of Discase Control, 2017). If an accurate prediction of pretreatment HIV RNA level is available, this would provide a useful tool in assisting selection of ABC or RPV in first-line regimen without performing measurement of pretreatment HIV RNAlevel. Hence, we sought to identify factors associated with pretreatment HIV RNA ≤100,000 copies/ml and to construct a predictive model for such a situation.

MATERIALS AND METHODS

Subjects

HIV-infected adults enrolled in TREAT (Therapeutics Research, Education, and AIDS Training) Asia HIV Observational Database (TAHOD), a prospective multicenter observational study of patients with HIV to assess the natural history of HIV disease in treated and untreated patients in the Asia and Pacific region (Zhou *et al*, 2005) were included. Patients from 21 clinical sites throughout 12 countries in Asia have been enrolled in the cohort since September 2003. Only HIV-infected patients from the four TAHOD sites in Thailand were enrolled, including patients from Faculty of Medicine Ramathibodi Hospital, Mahidol University not in TAHOD.

Data collection

HIV-infected adults (>15 years of age) were eligible if they had HIV RNA levels documented at or around the time of ART initiation (pretreatment HIV RNA level). The period of pretreatment HIV RNA measurement was between 3 months prior to and 1 day after the date of starting ART. Those exposed to mono- or dual-therapy prior to starting combination ART were excluded. Baseline characteristics were based on data of co-variables, *viz*. age, sex, HIV exposure, hepatitis B and C serology (if available), prior period of diagnosis of HIV infection, and HIV subtype, at date of ART initiation. The following co-variables were collected between 3 months prior and 3 months after the date of ART initiation: weight, body mass index (BMI), ane-

mia (hemoglobin level <13 g/dl for males, <12 g/dl for females), total lymphocyte count, CD4 count, and syphilis serology [positive rapid plasma reagin (RPR) or *Treponema pallidum* particle agglutination assay (TPHA)].

Data analysis

The data set was randomly splitted into a derivation data set (from 75% of eligible patients) and a validation data set (from 25% of eligible patients). The study endpoint was pretreatment HIV RNA ≤100,000 copies/ml. Factors associated with the endpoint were evaluated by logistic regression. Co-variables were considered for inclusion in the multivariate model if one or more categories exhibit(s) *p*-value <0.1 and excluded if one or more categories exhibit(s) *p*-value >0.05.

Prediction scores are created by multiplying the regression coefficient of each multivariate co-variable by 10 and rounding to the nearest integer (Moons *et al*, 2002). Discrimination is evaluated using an area under receiver operating characteristic (AUROC) curve (Hanley and McNeil, 1982). Patients who had available data for all variables were included in the prediction model. Optimal score cut-off point was evaluated based on sensitivity, specificity, positive predictive value, and negative predictive value. Stata version 12.0 (StataCorp, College Station, TX) was used for all statistical analysis.

RESULTS

Of 1,223 patients enrolled in the study, 873 patients were randomly allocated to the derivation and 350 to the validation groups. At start of ART median [interquartile range (IQR)] age was 36.3 (30.5-42.9) years, weight 54.5 (48.0-62.3) kg, and duration of HIV diagnosis 0.6 (0.1-3.0) years; 81.8% had heterosexual HIV exposure and 32.0% prior AIDS-defining illness (Table 1). Median (IQR) CD4 count was 122 (39-216) cells/mm^3 and pretreatment HIV RNA level 100,000 (32,449-229,777) copies/ml. Anemia was present in 79.6% of the patients, positive HBsAg in 8.8%, positive anti-HCV in 4.1%, positive syphilis serology in 2.2%, and HIV infection with the CRF01_AE subtype in 67.8%.

HIV patients with pretreatment HIV RNA levels ≤100,000 copies/ml were in the group with lower median age, higher median body weight group, longer median duration of HIV diagnosis, lower proportion of having prior AIDS-defining illness, less likely to have acquired HIV from heterosexual contact, higher median CD4 counts, higher median hemoglobin level, and higher total lymphocyte counts (Table 2). Univariate logistic regression analysis indicated factors significantly associated with pretreatment HIV RNA level ≤100,000 copies/ml are >35 years of age, having non-heterosexual contact, duration of HIV diagnosis >1 year, prior AIDS-defining illness, CD4 count >200 cells/mm^3, without anemia, and total lymphocyte count >1,500 cells/mm^3 (Table 3); multivariate logistic regression analysis revealed factors of significance being non-heterosexual HIV exposure, CD4 count ≥200 cells/mm^3 and without anemia (Table 3). When these latter three factors were included in the clinical prediction tool for pretreatment HIV RNA level ≤100,000 copies/ml, score (from a maximum of +23) was +5.0, +7.0 and +11.0 for non-heterosexual HIV exposure, non-anemia and CD4 count >200 cells/mm^3 (Table 4).

AUROC analysis for predicting pretreatment HIV RNA level ≤100,000 copies/ml resulted in 0.66 (95% CI: 0.62-0.69) among derivation patients and 0.62 (95% CI: 0.55-0.69) among validation patients (Fig 1). AUROC results are considered

Table 1
Baseline characteristics of HIV-infected patients (n = 873) enrolled in the study.

Baseline characteristic	Value (%)[a]
Median (IQR) age, years	36.3 (30.5-42.9)
Male	495 (56.7)
HIV exposure	
Heterosexual	714 (81.8)
Homosexual	118 (13.5)
Intravenous drug user	16 (1.8)
Others	25 (2.9)
Median (IQR) weight, kg	54.5 (48-62.3)
Median (IQR) duration of HIV diagnosis, years	0.6 (0.1-3.0)
≤1 year	368 (42.2)
>1 year	490 (56.1)
Missing	15 (1.7)
Prior AIDS-defining illness	
Yes	279 (32)
Not known	594 (68)
Median (IQR) CD4 count, cells/mm^3	122 (39-216)
≤200	583 (66.8)
>200	23 (27.2)
NA	53 (6.0)
Median (IQR) HIV RNA, copies/ml	100,000 (32,449-229,777)
Anemia	
Yes	671 (76.9)
No	122 (14.0)
NA	80 (9.1)
Median (IQR) total lymphocytes, cells/mm^3	1,450 (987-1,970)
≤1,500	419 (48.0)
>1,500	372 (42.6)
Missing	82 (9.4)
HBsAg	
Negative	670 (76.8)
Positive	77 (8.8)
NA	126 (14.4)
Anti-HCV	
Negative	588 (67.4)
Positive	36 (4.1)
NA	249 (28.5)
Syphilis serology	
Negative	285 (32.6)
Positive	19 (2.2)
NA	569 (65.2)
HIV subtype	
CRF01_AE	592 (67.8)
B	38 (4.4)
Others	27 (3.1)
NA	216 (24.7)

[a]Unless otherwise stated. Anti-HCV, hepatitis C antibody; HBsAg, hepatitis B surface antigen; IQR, interquartile range; NA, not available.

Table 2
Baseline characteristics of HIV-infected patients (n = 873) enrolled in the study stratified according to pretreatment HIV RNA level.

Baseline characteristic	HIV RNA >100,000 copies/ml Value (%)[a]	HIV RNA ≤100,000 copies/ml Value (%)[a]	p-value
Median (IQR) age, years	37.2 (31.3-43.2)	35.2 (29.7-42.1)	0.025
≤35	179 (40.6)	215 (49.8)	0.006
>35	262 (59.4)	217 (50.2)	0.222
Male	259 (58.7)	236 (54.6)	0.076
HIV exposure			
Heterosexual	374 (84.8)	340 (78.7)	
Homosexual	48 (10.9)	79 (16.2)	
Intravenous drug user	9 (2)	7 (1.6)	
Others	10 (2.2)	15 (3.5)	
Median (IQR) weight, kg	53 (47-61)	56.2 (48.5-63.4)	0.006
≤50	143 (37.9)	129 (32.1)	0.087
>50	234 (62.1)	273 (67.9)	
Median (IQR) duration of HIV diagnosis, years	0.4 (0.2-2.7)	0.8 (0.1-3.6)	0.029
≤1 year	266 (61.4)	224 (52.7)	0.010
>1 year	167 (38.6)	20 (47.3)	
Prior AIDS-defining illness	169 (38.3)	110 (25.5)	<0.001
Median (IQR) CD4 count, cells/mm^3	77.5 (27-171)	175.5 (59-248)	<0.001
≤200	337 (82.2)	246 (60)	<0.001
>200	73 (17.8)	164 (40)	
Median (IQR) hemoglobin level, g/dl	11.5 (10.2-12.9)	12.3 (11.1-13.8)	<0.001
Anemia	348 (90.2)	323 (79.4)	<0.001
Median (IQR) total lymphocyte counts, cells/mm^3	1,240 (820-1,726)	1,628 (1,229-2,123)	<0.001
≤1,500	247 (63.5)	172 (42.8)	<0.001
>1,500	42 (36.5)	230 (57.2)	0.656
HBsAg			
Positive	36 (8.2)	41 (9.5)	
Negative	344 (78)	326 (75.5)	
NA	61 (13.8)	65 (15)	
Anti-HCV			0.502
Positive	19 (4.3)	17 (3.9)	
Negative	304 (68.9)	284 (65.8)	
NA	118 (26.8)	131 (30.3)	
Syphilis serology			0.147
Positive,	8 (1.8)	11 (2.6)	
Negative	157 (35.6)	128 (29.6)	
NA	276 (62.6)	293 (67.8)	
HIV subtype			0.487
CRF01_AE	304 (90.5)	288 (89.7)	
B	21 (6.2)	17 (5.3)	
Others	11 (3.3)	16 (5)	

[a]Unless otherwise stated. Anti-HCV, hepatitis C antibody; HBsAg, hepatitis B surface antigen; IQR, interquartile range; NA, not available.

Table 3
Factors associated with pretreatment HIV RNA level ≤100,000 copies/ml in derivation patients (n = 873) enrolled in the study.

Factor	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value
Age >35 years *vs* ≤35 years	0.69 (0.53-0.90)	0.007		
Male	0.85 (0.65-1.11)	0.222		
Non-heterosexual HIV exposure	1.51 (1.07-2.14)	0.020	1.6 (1.07-2.43)	0.021
Weight >50 kg *vs* ≤50 kg	1.29 (0.96-1.74)	0.088		
Duration of HIV diagnosis >1 year *vs* <1 year	1.43 (1.09-1.88)	0.010		
Prior AIDS-defining illness	0.55 (0.41-0.73)	<0.001		
CD4 count >200 *vs* ≤200 cells/mm^3	3.08 (2.23-4.24)	<0.001	3.00 (2.08-4.32)	<0.001
Without anemia	2.38 (1.58-3.60)	<0.001	2.05 (1.28-3.27)	0.003
Total lymphocyte counts >1,500 cells/mm^3 *vs* ≤1,500 cells/mm^3	2.32 (1.75-3.20)	<0.001		
Positive HBsAg	1.07 (0.89-1.29)	0.443		
Positive anti-HCV	1.09 (0.94-1.26)	0.267		
Positive syphilis serology	1.14 (0.99-1.31)	0.076		

Anti-HCV, hepatitis C antibody; HBsAg, hepatitis B surface antigen; OR, odds ratio.

Table 4
Clinical prediction tool for pretreatment HIV RNA ≤100,000 copies/ml of Thai HIV patients.

Variable	Score
Non-heterosexual HIV exposure	5
Heterosexual HIV exposure	0
CD4 count >200 cells/mm^3	11
CD4 count ≤200 cells/mm^3	0
Without anemia	7
Anemia	0
Maximum score	23

excellent for values of 0.9-1.0, good if 0.8-0.9 and fair if 0.7-0.8 (Obuchowski, 2003; Lüdemann *et al*, 2006).

A cut-off total score >16 yielded 10.8%, 97.3%, 80.8%, and 51.0% for sensitivity, specificity, positive predictive value, and negative predictive value for pretreatment HIV RNA level ≤100,000 copies/ml among derivation patients (Table 5).

DISCUSSION

To the best of our knowledge, this is the first study of a prediction tool for pretreatment HIV RNA level in treatment-naïve HIV-infected patients in Thailand. The study demonstrates factors associated with this parameter were non-heterosexual HIV exposure, CD4 counts >200 cells/mm^3 and non-anemic condition. A prediction tool generated from these variables resulted in an AUROC curve of 0.66, and with a cut-off score >16 yielded a sensitivity of 10.8% and specificity of 97.3%.

HIV treatment program begins with a diagnosis of HIV infection, followed by linkage to care (Kay *et al*, 2016). The care program for men who have sex with

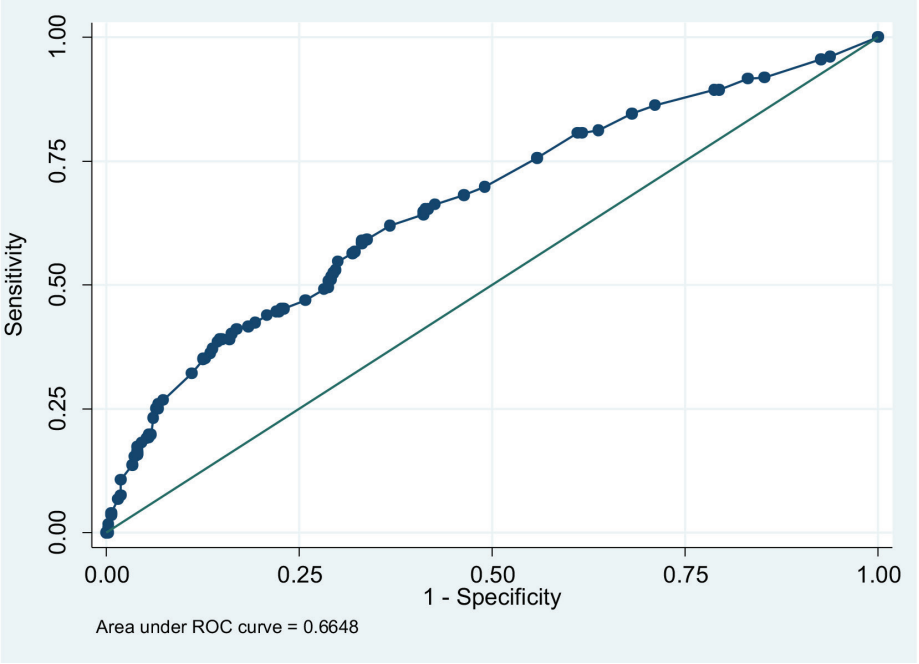

Fig 1 - Receiver operating characteristic (ROC) curve for predicting pretreatment HIV RNA ≤100,000 copies/ml among derivation HIV patients (n = 873) enrolled in the study. It is a plot of the sensitivity and false positive rate (1-specificity) for the differenent possible cutpoints of the score for predicting pretreatment HIV RNA ≤100,000 copies/ml among 873 derivation HIV patients.

Table 5
Sensitivity, specificity, positive predictive value and negative predictive value of a clinical prediction tool for pretreatment HIV RNA ≤100,000 copies/ml among derivation HIV patients (n = 873) enrolled in the study.

CPT score	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
>0	62.5	62.3	63.5	61.3
>7	41.3	82.4	71.1	57.2
>16	10.8	97.3	80.8	51.0

CI, confidence interval; CPT, clinical prediction tool; NPV, negative predictive value; PPV, positive predictive value.

men (MSM) shows similar or better care outcome compared with other individuals with HIV (Lourenço *et al*, 2014). HIV awareness among MSM in the United States has increased over time (Wejnert *et al*, 2013). This might be the reason why, among our patients, non-heterosexual HIV exposure (majority with homosexual HIV exposure) was associated with pretreatment HIV RNA level ≤100,000 copies/ml compared to heterosexuals exposed to HIV risk.

Low CD4 count is significantly associated with disease progression after HIV infection (Goujard *et al*, 2006; Phillips and Lundgren, 2006), and HIV RNA level correlates with decline in CD4 counts over time; for example, an average of 1 $\log_{10}$ increase in HIV RNA level result in a decrease in CD4 count of 46-55 cells/mm^3 (Lima *et al*, 2009; Phillips *et al*, 2010). Patients with higher CD4 counts reflect an early stage of HIV infection and concomitant lower HIV RNA levels, as observed in our study.

Anemia is a common condition among HIV-infected patients, especially in individuals with an advanced stage of HIV infection, possibly due to the patients' state chronic, nutritional deficiency and opportunistic infections impacting the bone marrow (Volberding *el al*, 2004). Increased risk of anemia is observed together with CD4 count <200 cells/mm^3 and increase in HIV RNA level (Mocroft *et al*, 1999; Semba *et al*, 2002). In addition, anemia is one of the independent factors for death among HIV-infected patients (Mocroft *et al*, 1999; Mekonnen *et al*, 2003). 'Without anemia' status was associated with pretreatment HIV RNA level <100,000 copies/ml, indicative of an early stage of HIV infection.

Strength of this study resides in the characteristics of the study population being close to those in real-life settings. We aimed to produce a guide for health care providers in resource-limited regions without availability to pretreatment HIV RNA measurements in selecting ABC or RPV in the first-line ART regimen. Our clinical prediction algorithm would serve as a prototype for an HIV RNA level prediction tool, with a score obtained from easily available parameters, such as route of HIV transmission, CD4 count and anemia status. These data are regularly recorded, reliable and used in clinical practice where pretreatment HIV RNA results are not available. We chose a score of >16 as the cut-off point as it yielded the highest specificity, necessary to minimize false positive results.

The main limitations of the study were (i) a number of patients were excluded from the regression analysis and from the prediction tool due to missing data; (ii) the poor performance of the model, as illustrated by AUROC of 0.66 that might be associated with the small sample size of the study population; and (iii) some factors associated with baseline HIV viral load were not included in the model, *eg* prior AIDS-defining illness, possibly accounting the low AUROC value.

In conclusion, this study highlights those factors associated with pretreatment HIV RNA ≤100,000 copies/ml and creates a clinical prediction tool applicable to resource-limited settings where HIV RNA measurement is not available. However, the performance of the model, based on AUROC value, was not sufficiently robust to allow prediction of the desired pretreatment HIV RNA levels among Thai HIV-infected patients. Determination of pretreatment HIV RNA levels remains necessary prior to initiation of ABC (except in combination with dolutegravir/3TC) or RPV in treatment-naïve HIV-infected patients. Further studies on a larger population with a greater diversity of data variables will be required to improve the present model.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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