Practice of Epidemiology

The Cerebrospinal Fluid HIV Risk Score for Assessing Central Nervous System Activity in Persons With HIV

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Detectable human immunodeficiency virus (HIV) RNA in the cerebrospinal fluid (CSF) is associated with central nervous system (CNS) complications. We developed the CSF HIV risk score through prediction modeling to estimate the risk of detectable CSF HIV RNA (threshold >50 copies/mL) to help identify persons who might benefit most from CSF monitoring. We used baseline data from 1,053 participants receiving combination antiretroviral therapy who were enrolled in the 6-center, US-based CNS HIV Antiretroviral Therapy Effects Research (CHARTER) prospective cohort in 2004–2007. Plasma HIV RNA, CNS penetration effectiveness, duration of combination antiretroviral therapy, medication adherence, race, and depression status were retained correlates of CSF HIV RNA, displaying good discrimination (*C* statistic = 0.90, 95% confidence interval (CI): 0.87, 0.93) and calibration (Hosmer-Lemeshow *P* = 0.85). The CSF HIV risk score ranges from 0 to 42 points, with a mean of 15.4 (standard deviation, 7.3) points. At risk scores greater than 25, the probability of detecting CSF HIV RNA was at least 42.9% (95% CI: 36.6, 49.6). For each 1-point increase, the odds of detecting CSF HIV RNA increased by 26% (odds ratio = 1.26, 95% CI: 1.21, 1.31; *P* < 0.01). The risk score correlates with detection of CSF HIV RNA. It represents an advance in HIV management and monitoring of CNS effects, providing a potentially useful tool for clinicians.

central nervous system; cerebrospinal fluid; cerebrospinal fluid human immunodeficiency virus risk score; human immunodeficiency virus; prediction model

Abbreviations: AIDS, acquired immune deficiency syndrome; cART, combination antiretroviral therapy; CHARTER, Central Nervous System Human Immunodeficiency Virus Antiretroviral Therapy Effects Research; CI, confidence interval; CNS, central nervous system; CPE central nervous system penetration effectiveness; CSF, cerebrospinal fluid; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; HAND, human immunodeficiency virus–associated neurocognitive disorder; HIV, human immunodeficiency virus; SD, standard deviation.

The introduction of combination antiretroviral therapy (cART) has improved survival and reduced opportunistic infections in persons infected with human immunodeficiency virus (HIV) (1). cART has also been associated with a greatly reduced incidence and phenotypical severity of human immunodeficiency virus–associated neurocognitive disorder (HAND), although milder forms of HAND have increased in prevalence (2–4). Even though cART use improves cognition, a significant percentage of patients develop new cognitive impairment or depression during treatment (5). This is important because neurocognitive impairment and depression are both associated with poor HIV outcomes and substantially worse survival rates (6–8).

HIV infection in the central nervous system (CNS) may be associated with glial and endothelial activation resulting in inflammatory and degenerative insults that lead to neuronal injury and neurocognitive impairment (9–11). HIV viral replication in the cerebrospinal fluid (CSF) is hypothesized to be clinically relevant to neurological and psychiatric complications of HIV. Residual CSF viral replication in patients with

undetectable plasma HIV RNA or CSF HIV RNA concentration ≥1 log higher than plasma HIV RNA concentration, called CSF viral escape, is estimated to occur in more than 10% of patients and is considered clinically relevant by several groups across United States and Europe (10, 12, 13). CSF viral escape has been associated with HAND, depression, and neurological deficits in HIV patients (9, 10, 14).

Recent findings suggest CSF testing to examine residual viral activity, immune activation, and neural damage in managing HAND (15). The 2013 European Acquired Immune Deficiency Syndrome (AIDS) Clinical Society also provides guidelines for measuring CSF HIV RNA levels as a component of their clinical strategy for managing HAND (16). The MIND Exchange Program, in a recent consensus report, recommends CSF testing for HIV RNA in persons with suspected or demonstrated neurocognitive impairment (17).

Some antiretroviral drugs are hypothesized to be more neurologically active than others on the basis of their ability to penetrate the CNS and effectively suppress virus replication as reflected by reductions in CSF HIV RNA (18, 19). Improvement in cognition with higher CNS-penetrating drugs and suppression of CSF HIV RNA are hypothesized to be primary modulators of favorable neurological response in HIV patients (20, 21). CSF analysis is useful to assess the activity of HIV in the CNS as reflected by detectable HIV RNA (15). Poor cART penetration of the blood-brain barrier and active efflux systems that reduce the parenchymal concentration of cART may allow HIV replication to continue in the CNS despite peripheral suppression (22).

Because lumbar punctures may pose a resource utilization challenge in HIV clinics worldwide and are not without risks, we developed an algorithm to determine correlates (referred to herein as "predictors") of detectable CSF HIV RNA during HIV treatment using readily attainable clinical and demographic data that would be useful for clinical management of HIV. We accomplished this by using data from the Central Nervous System Human Immunodeficiency Virus Antiretroviral Therapy Effects Research (CHARTER) Study cohort.

METHODS

Study design and patients

The CHARTER Study is a 6-center, US-based, prospective observational study that started in 2004 and is designed to comprehensively assess a representative US clinical population of persons who are HIV seropositive (23). There were no general exclusion criteria except the inability to consent to participation in study assessments. The CHARTER Study aimed to evaluate the changing presentation of neurological complications of HIV in the context of cART. Study sites include Johns Hopkins University (Baltimore, Maryland), Icahn School of Medicine at Mt. Sinai (New York, New York), University of California (San Diego, California), University of Texas (Galveston, Texas), University of Washington (Seattle, Washington), and Washington University (St. Louis, Missouri). The institutional review board at each study site or the Western Institutional Review Board (Puyallup, Washington) approved the study.

We analyzed data from 1,053 of 1,561 CHARTER Study participants who were currently receiving cART at study entry between 2004 and 2007. Because we sought to examine correlates of the presence of CSF HIV RNA in persons receiving cART, we excluded all participants who were not receiving cART at study entry (n = 508). A total of 1,053 persons receiving cART were included in these analyses. Participants underwent extensive evaluation, including HIV and treatment history verified by medical records, physical examination, lumbar puncture, and venipuncture.

Diagnostic predictors of CSF HIV

Potential predictors included patient demographic characteristics and HIV treatment–related data, including current and nadir CD4+ T-cell counts, plasma and CSF HIV RNA levels, duration of HIV seropositivity, duration and type of cART regimens (i.e., protease inhibitor– vs. nonnucleoside reverse transcriptase inhibitor–based regimens), medication adherence assessed by the AIDS Clinical Trials Group 4-Day Adherence Questionnaire (24), number of drugs, and central nervous system penetration effectiveness (CPE) scores of current and past cART regimens, which are an estimate of the CNS penetration of cART (10). The CPE score ranks individual antiretroviral medications from 1–4, with higher scores reflecting greater CNS penetration. Derivation of the class of penetration is based on 1) chemical properties suggesting the extent of penetration; 2) concentration of the drug in the CSF based on human and animal studies or comparison of the CSF concentration of the drug compared with half the maximum inhibitory concentration, a measure of the extent to which the anti-HIV drug is effective in inhibiting the virus; and 3) demonstrated effectiveness in reducing CSF viral load or improving cognition in clinical studies (25). The concept of CPE scores circumvents the direct measurement of CSF drug concentrations, but may not accurately correlate with the CNS concentrations of anti-HIV drugs. Appendix Table 1 shows the CPE scores of frequently used antiretroviral drugs (10).

Other potential predictors included the Global Deficit Score, a validated measure that is derived from the standardized, comprehensive neurocognitive assessment and summarizes overall functioning across 7 cognitive abilities (26); major depressive episode within last 30 days assessed by *Diagnostic Statistical Manual, Fourth Edition*, (DSM-IV) criteria (27); Beck Depression Inventory score (28); history of opportunistic infection; and hepatitis C virus seropositivity. Information on illicit substance use and abuse was obtained by using the Composite International Diagnostic Interview of the DSM-IV.

Outcome

The outcome was the presence of CSF HIV RNA at a threshold of 50 copies/mL. Both CSF and plasma HIV RNA levels were determined by commercial ultrasensitive reverse transcriptase-polymerase chain reaction (AMPLICOR, Roche Diagnostics, Indianapolis, Indiana).

Statistical analysis

The population characteristics were examined by using summary statistics. We fit a stepwise backwards multivariable

Table 1.   Characteristics of Individuals Receiving Combination HIV Therapy at Study Entry in the CHARTER Study Cohort, 2004–2007

Characteristic	Total No.	Distribution of Participant Characteristics			
		Group No.	%	Mean (SD)	Median (IQR)
Age, years	1,053			44.3 (8.0)	
Male sex	1,053	822	78.1		
Race	1,053				
White		414	39.2		
Black		504	49.7		
Hispanic/other		135	12.8		
Education, years	1,053			12.6 (2.5)	
CD4 T-cell nadir, cells/mm^3	1,053			150.6 (147.1)	120.0 (29.0–218.0)
Current CD4 T-cell count, cells/mm^3	1,042			458.0 (290.7)	418.5 (248.0–610.0)
Log plasma HIV RNA, copies/mL	1,040			2.35 (1.04)	1.70 (1.70–2.70)
Log CSF HIV RNA, copies/mL	811			1.86 (0.49)	1.70 (1.70–1.70)
CSF HIV virus present	811	127	15.7		
HIV regimen type	1,053				
NNRTI based		362	34.4		
PI based		599	56.9		
PI/NNRTI based		54	5.1		
Other		36	3.6		
No. of HIV drugs	1,053				
3		794	75.4		
>3		259	24.6		
CPE score	1,053			7.3 (1.7)	
HIV medication adherence, %	1,045				
≥95		915	87.6		
85–94		46	4.4		
<85		84	8.0		
HCV positive	1,034	275	26.6		
Total Beck Depression Inventory II score (28)	1,044			13.9 (10.8)	
Current depression[a] diagnosis within last 30 days	1,049	140	13.4		
Beck Depression Inventory II score >14	1,044	459	44.0		
Lifetime depression	1,049	527	50.2		
Duration of current treatment, months	1,041			20.6 (23.0)	
Duration of HIV infection, months	1,050			130.1 (72.6)	
Any opportunistic infection	1,053	150	14.3		

Abbreviations: CHARTER, Central Nervous System Human Immunodeficiency Virus Antiretroviral Therapy Effects Research; CPE, central nervous system penetration effectiveness; CSF, cerebrospinal fluid; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SD, standard deviation.

[a] Depression assessed by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (27).

logistic regression model (29), the outcome being detectable CSF HIV RNA. Variables associated with detectable CSF HIV were retained at a significance level of 0.157, which equates to the Akaike information criterion for selection of a single predictor (30). Selection at this level rather than conventional significance levels reduces selection bias, thus preventing overestimated regression coefficients, and diminishes optimism from overfitting of the data, which results in poor prediction in independent data.

Transformed continuous variables were compared with linear forms to determine the best-fitting functional forms to be included in the final model (29, 31). Continuous forms of all variables were preferentially fitted in regression models because of the advantage of creating robust regression
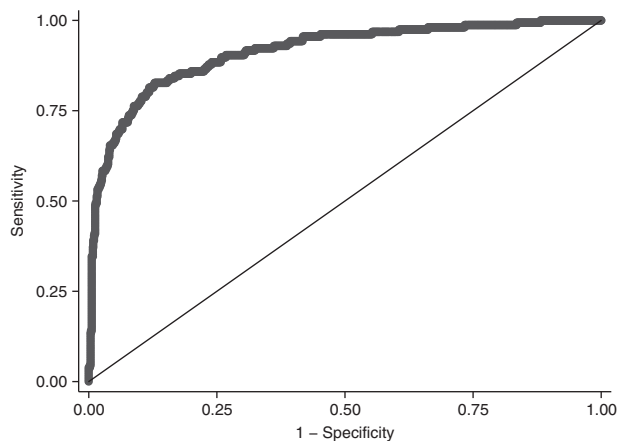
Figure 1.   Discrimination plot of the cerebrospinal fluid (CSF) human immunodeficiency virus (HIV) risk score, Central Nervous System Human Immunodeficiency Virus Antiretroviral Therapy Effects Research (CHARTER) cohort at study entry, 2004–2007. The discrimination plot shows the plot of sensitivity versus 1 – specificity of the CSF HIV risk score indicated by the curved line. The diagonal line shows the noninformative line where sensitivity is equal to specificity. The area under the curve = 0.90 (95% confidence interval: 0.87, 0.93) and represents the discriminative ability of the test to correctly differentiate between 2 individuals, 1 with detectable CSF HIV RNA and the other without detectable CSF HIV RNA.

models compared with using relatively arbitrary cut-points of categorization (30).

The accuracy of the retained model was assessed and compared by forcing in specific variables and reducing the selected model. Discrimination was assessed by the receiver operator curve *C* statistic (32), a measure of chance that the prediction model will assign a higher probability to a patient
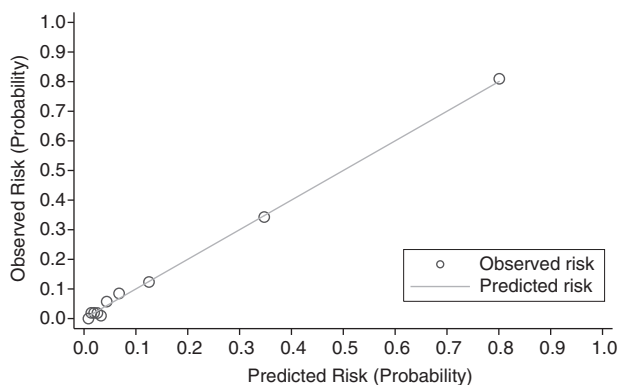

Figure 2.   Calibration plot of the cerebrospinal fluid (CSF) human immunodeficiency virus (HIV) risk score, Central Nervous System Human Immunodeficiency Virus Antiretroviral Therapy Effects Research (CHARTER) cohort at study entry, 2004–2007. The *x*-axis shows the risk (probability) of detectable CSF HIV RNA as predicted by the CSF HIV risk score. The *y*-axis shows the observed risk in the CHARTER cohort. Circles represent a risk class with corresponding predicted and observed risk. The solid line represents perfect agreement (Hosmer-Lemeshow *P* = 0.85) and tests whether predicted and observed risks differ significantly across classes.

with detectable CSF HIV RNA compared with a patient without detectable CSF HIV RNA. We assessed model calibration by the Hosmer-Lemeshow test (33), which compares the observed and predicted probabilities of detectable CSF HIV RNA in various risk classes in the study population.

Internal validation was performed by 5-fold cross-validation and bootstrapping techniques (29). To prevent our model from being overly optimistic in future applications, we calculated shrunken estimates by applying the calculated Van Houwelingen and Le Cessie heuristic shrinkage estimator (34). To enhance the future application of our findings in clinical settings, we used the risk score approach to apply points to the final prediction model (31). We calculated the predicted probability estimates of detectable CSF HIV RNA for the logistic regression model provided by $P = 1/[1 + \exp(-\sum \beta_i X_i)]$ (31).

We examined the distribution of CSF viral load by risk score category and fit logistic regression models to examine the odds of detectable CSF HIV RNA per 1-, 5-, and 10-point increase in risk score. Missing data were handled by multivariate imputation using chained equations by linear and augmented logistic regression (35) imputing the median of 50 values generated from each observation (36). We performed model checking, diagnostic procedures, and sensitivity analyses (the latter are included in Appendix 2). We examined interactions between cART adherence and CPE of current cART, as well as cART adherence and months on cART, and we evaluated discriminatory performance by receiver operator curve comparisons to assess whether the difference in performance of the various models was 0. To evaluate the utility of the retained potential predictors in persons with plasma HIV RNA less than 10,000 copies/mL or less than 50 copies/mL, we examined discriminatory performance in these subpopulations.

Because the CPE score is an estimate of the extent to which cART penetrates the CNS, we also examined its discriminatory and calibration performance to potentially predict detectable CSF HIV RNA. E.R.H. performed the statistical analysis with Stata, version 12, statistical software (StataCorp LP, College Station, Texas).

RESULTS

Demographic and clinical characteristics of participants included in our analysis are displayed in Table 1. The mean age was 43.3 years, and 78% of participants were male. A total of 39.2% of participants were white, 49.7% were black, and 12.8% were Hispanic. The mean duration of cART usage was 20.6 (standard deviation (SD), 23.0) months, and the mean duration of HIV seropositivity was 130.1 (SD, 72.6) months. Prior diagnosis of opportunistic infection was reported in 14.3% of subjects, and 13.4% of subjects met DSM-IV criteria for current depression. Overall, CSF HIV RNA was detectable (at 50 copies/mL) in 15.7% of subjects (127 of 811).

In multivariable logistic regression analysis, CPE, race, depression, plasma HIV RNA, duration of cART, and cART adherence were retained as correlates of detectable CSF HIV RNA. There were no interactions between cART

Table 2.   Regression Coefficients, Odds Ratios and Development of the CSF HIV Risk Score[a] in the CHARTER Study Cohort at Study Entry, 2004–2007

Variable	Regression Coefficient	Odds Ratio	95% CI	P Value	Shrunken[b] Regression Coefficient β_i	Reference Value W_{ij} (Midpoint)	β_i (W_{ij}-W_{iRef})	Risk Score ($\beta_i \times$ [(W_{ij}-W_{iRef})]/B^c)
CPE score	−0.266[d]	0.77	0.67, 0.88	<0.001	−0.249			
≥10						12 (W_{1Ref})	0	0
5–9						7	1.245	6
<5						4	1.992	9
Race								
White		1.00	Referent			0 (W_{2Ref})	0	0
Black	0.593	1.81	1.06, 3.09	0.02	0.556	1	0.556	3
Hispanic/other	0.875	2.39	1.16, 4.95	0.02	0.820	1	0.820	4
Current depression								
No		1.00	Referent			0 (W_{3Ref})	0	0
Yes	0.808	2.25	1.18, 4.28	0.01	0.757	1	0.757	4
HIV medication adherence, %								
≥95		1.00	Referent			97.5 (W_{4Ref})	0	0
85–94	0.584	1.79	0.67, 4.79	0.23	0.547	89.5	0.547	3
<85	0.599	1.82	0.90, 3.68	0.10	0.561	80.0	0.561	3
Log plasma RNA, copies/mL	1.584[d]	4.88	3.91, 6.09	<0.001	1.486			
<1.699						1.699 (W_{5Ref})	0	0
1.699–2.299						1.999	0.446	2
2.301–3.999						3.150	2.156	10
>4.0						5.627	3.928	18
Current cART, months	−0.011[d]	0.99	0.98, 1.00	0.07	−0.010			
≥36						75 (W_{6Ref})	0	0
25–35						30	0.450	2
13–24						18	0.570	3
7–12						9	0.660	3
≤6						3	0.720	4

Abbreviations: cART, combination antiretroviral therapy; CHARTER, Central Nervous System Human Immunodeficiency Virus Antiretroviral Therapy Effects Research; CI, confidence interval; CNS, central nervous system; CPE, central nervous system penetration effectiveness; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus.

[a] Under the points system, meaningful categories of predictors were created, and the distance from a chosen reference category was determined in regression units. Integer points were assigned to each level of predictor, and the risk estimate was determined from total points assigned by a reference table (30). Points were rounded to the next integer.

[b] Regression coefficients were multiplied by a shrinkage factor of 0.937.

[c] B represents the constant for the point system or the number of regression units that will correspond to 1 point. The constant reflects the risk of detecting CSF HIV RNA associated with the study population's mean duration on cART, 20.6 months ($B = 20.6 \times 0.011 = 0.227$).

[d] Regression coefficient for continuous form of variable.

adherence and CPE of current cART or of cART adherence and months on cART. Five-fold cross-validation displayed very good discrimination (C statistic = 0.90, 95% confidence interval (CI): 0.87, 0.93 for the full model) (Figure 1). The calibration plot for the full model demonstrates that predicted probabilities were similar to observed probabilities (Hosmer-Lemeshow $P = 0.85$) (Figure 2). Further internal validation by bootstrapping methods correcting for model optimism (e.g., overfitting of data) displayed good discrimination

(C statistic = 0.84, 95% CI: 0.81, 0.87). Average optimism was 0.074. The mean variance inflation factor, a measure of how predictor variables are correlated, was 1.03. When we examined the performance of the CPE score alone in potentially predicting detectable CSF HIV RNA, we observed a lower discrimination and calibration performance (C statistic = 0.55, 95% CI: 0.5, 0.61; Hosmer-Lemeshow $P = 0.008$). The discriminatory ability, C statistic, of retained correlates of CSF HIV RNA among person with plasma HIV RNA levels less

Table 3.   Predicted Probabilities of Detectable CSF HIV RNA (at >50 copies/mL) by the CSF HIV Risk Score in 811 Persons Receiving Combination Antiretroviral Therapy at Study Entry, CHARTER Study Cohort, 2004–2007

CSF HIV Risk Score	Predicted Probability, %	95% CI
0	0.24	0.11, 0.53
5	0.75	0.40, 1.4
10	2.32	1.5, 3.7
15	7.0	5.1, 9.5
20	19.2	15.7, 23.2
25	42.9	34.6, 49.6
30	70.3	61.5, 77.9
35	88.2	81.2, 92.9
39	95.0	90.5, 97.4

Abbreviations: CHARTER, Central Nervous System Human Immunodeficiency Virus Antiretroviral Therapy Effects Research; CI, confidence interval; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus.

Figure 3.   Predicted probabilities and 95% confidence intervals (CIs) of detectable cerebrospinal fluid (CSF) human immunodeficiency virus (HIV) RNA by the CSF HIV risk score, Central Nervous System Human Immunodeficiency Virus Antiretroviral Therapy Effects Research (CHARTER) cohort at study entry, 2004–2007.

than 10,000 copies/mL was 0.84 (95% CI: 0.79, 0.89; Hosmer-Lemeshow $P = 0.69$). Among persons with plasma HIV RNA of less than 50 copies/mL, the discriminatory ability was 0.70 (95% CI: 0.55, 0.85; Hosmer-Lemeshow $P = 0.08$). The discriminatory ability of detectable plasma HIV RNA alone was lower compared with the full retained model (C statistic = 0.72, 95% CI: 0.64, 0.80). A calibration plot of plasma HIV RNA alone revealed that predicted probabilities were significantly different from observed probabilities, indicating poor model fit (Hosmer-Lemeshow $P = 0.009$).

Table 2 summarizes the development of the CSF HIV risk score. The observed predictor variable coefficients were multiplied by the calculated shrinkage factor 0.937 to prevent overfitting if this model should be applied to another population. Model fit due to noise was 6.3%.

The CSF HIV risk score ranges from 0 to 42 points. In our study population, the risk score ranged from 0 to 39 points with a mean of 15.4 (SD, 7.3) points. The largest potential predictor of detectable CSF HIV was plasma HIV RNA at levels greater than 10,000 copies/mL, contributing 42.9% (18 points) of the maximum possible total risk score.

The predicted probabilities of detectable CSF HIV RNA in persons receiving cART for various levels of the CSF HIV risk score are displayed in Table 3 and Figure 3. For example, a black patient (3 points) with plasma HIV RNA of 300 copies/mL (10 points), who is presently depressed (4 points), and is fully adherent to the cART regimen (0 points), whose regimen has a total CPE of 9 (6 points) for a duration of 10 months (4 points) has a total CSF HIV RNA score of 27 points and a 54.3% (95% CI: 46.5, 62.0) probability of having detectable CSF HIV RNA. At risk scores greater than 25, the observed probability of detecting CSF HIV RNA is at least 42.9% (95% CI: 36.6, 49.6).

We observed a dose-response association between increasing CSF HIV risk score category and increasing CSF viral load (Table 4, Figure 4). For each 1-point increase on the risk score, the odds of detecting CSF HIV RNA increased by 26% (odds
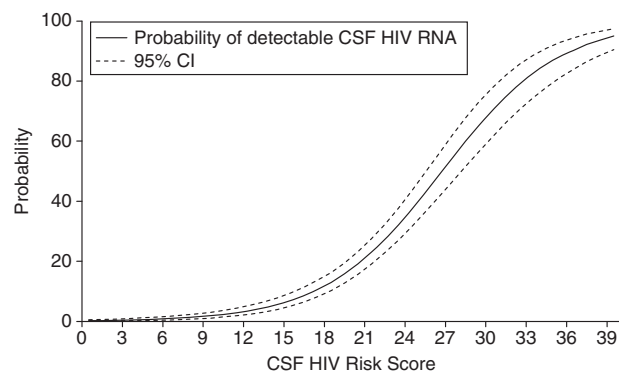
ratio = 1.26, 95% CI: 1.21, 1.31; $P < 0.001$) (Figure 5). Likewise, increases in risk score of 5 and 10 points were associated with a 3-fold increase in odds (odds ratio = 3.16, 95% CI: 2.64, 3.79; $P < 0.001$) and a 9-fold increase in odds (odds ratio = 9.99, 95% CI: 6.95, 14.1; $P < 0.001$), respectively.

DISCUSSION

We developed a CSF HIV risk score (Hammond score) to potentially predict the probability of identifying detectable CSF HIV RNA in persons receiving cART. This score may provide a practical means to estimate the probability of finding CSF HIV RNA, thus providing a meaningful tool for providers to use when discussing the utility of performing a lumbar puncture. Measures of predicting CSF HIV RNA have not been previously described, so our findings contribute substantially to the field and may allow meaningful inferences to be drawn in HIV management.

The CSF HIV risk score displayed high predictive accuracy with 2 robust internal validation techniques: cross-validation performance of 0.90 and bootstrapped performance with correction for optimism of 0.84. This can be interpreted as at least an 84% probability that the CSF HIV risk score will assign a higher probability of detecting CSF HIV RNA in a patient with positive CSF HIV than in a patient with undetectable CSF HIV RNA.

Our prediction tool holds promise for the clinical management of HIV. It relies on measurements that are readily available: plasma HIV RNA, CPE, duration of current cART regimen, cART adherence, race, and depression status. The mean variance inflation factor of 1.03 suggests no collinearity between predictor variables, an indication that each variable contributes sufficiently and independently toward potentially predicting detectable CSF HIV RNA. To the clinician, this may suggest that addressing modifiable factors may reduce the risk of persistent detectable CSF HIV RNA, which several studies have indicated to be harmful (10, 37).

A model with plasma HIV RNA alone as a predictor of detectable CSF HIV RNA was not well calibrated. Because of

Table 4.   Distribution of CSF Viral Load by CSF HIV Risk Score Category in 811 Persons With HIV at Study Entry, CHARTER Study Cohort, 2004–2007

Category	Risk Score	No. of Subjects	Log^{10} CSF Viral Load, mean (SD)	P Value for Comparison of CSF HIV Risk Score Categories			
				Versus Category 1	Versus Category 2	Versus Category 3	Versus Category 4
1	0–10	217	0.1099 (0.4146)		0.080	<0.001	<0.001
2	11–20	404	0.2716 (0.6800)	0.080		<0.001	<0.001
3	21–30	145	1.4934 (1.1495)	<0.001	<0.001		<0.001
4	31–39	45	2.7313 (1.2672)	<0.001	<0.001	<0.001	

Abbreviations: CHARTER, Central Nervous System Human Immunodeficiency Virus Antiretroviral Therapy Effects Research; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; SD, standard deviation.

variability among patients, including clinical presentation, health behavior, and other health states, a single predictor variable is rarely of adequate prognostic value and may be misinforming even if it displays sufficient discrimination (29, 38, 39). The use of multivariable design and analyses is essential for prediction models with a goal to construct accurate and discriminating models. At plasma HIV RNA levels of less than 10,000 copies/mL, each potential predictor variable in the final regression model contributes substantially to assessing CSF HIV risk. Because retained predictors of detectable CSF HIV RNA showed good discriminatory performance at plasma HIV RNA levels of less than 10,000 copies/mL, and plasma HIV RNA alone did not yield good model fit, it may suggest that, below this threshold, routine monitoring of plasma HIV RNA alone may not be a sufficient surrogate for estimating CSF HIV activity, supporting previous findings of CSF viral escape in persons with undetectable plasma virus (13, 40). Consequently, it is likely that the risk score has utility even when plasma HIV RNA is not detectable.

Although routine plasma HIV RNA monitoring is recommended as standard of care (41), an increased CSF HIV risk score may suggest which patients will benefit from CSF HIV RNA monitoring. Application of this risk score may better focus resources to enable cost-effective monitoring of CNS disease.

When clinical deterioration is noticed in a previously stable patient, the risk score can be applied to provide insight into potential CNS HIV disease activity. Such assessments may necessitate an informed clinical decision to request CSF examination, including measurement of HIV RNA, immune activation, and viral resistance. The risk score can also be monitored during alteration of therapy. An assessment of the probability of detectable CSF HIV RNA may also facilitate measures to alter modifiable factors such as the CPE of the cART regimen, cART adherence, and depression.

Depression is the most common psychiatric disorder associated with HIV. In persons with HIV infection, depression has been associated with lower CD4+ cell counts, immune activation, and increased risk of death, whereas resolution of depression is associated with increased natural killer cell activity (7, 42). Our findings suggest that effectively treating
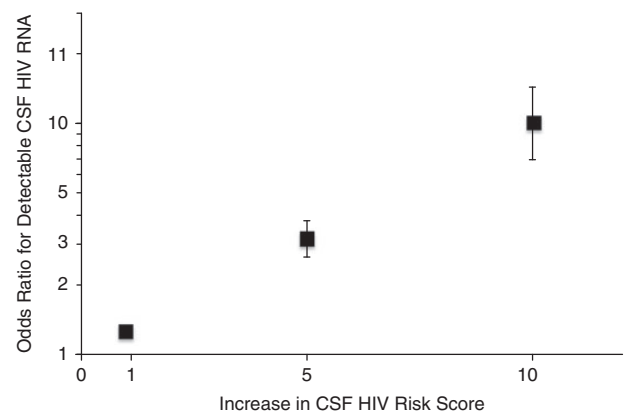

Figure 4.   Distribution of cerebrospinal fluid (CSF) human immunodeficiency virus (HIV) RNA viral load by category of CSF HIV risk score, Central Nervous System Human Immunodeficiency Virus Antiretroviral Therapy Effects Research (CHARTER) cohort at study entry, 2004–2007, (n = 811). P < 0.001 comparing CSF HIV risk score category 2 versus categories 3 and 4; P < 0.001 comparing CSF risk score category 3 versus categories 1, 2, and 4; and P < 0.001 comparing CSF risk score category 4 versus 1, 2, and 3. Participants per risk score category: category 1 = 217; category 2 = 404; category 3 = 145; and category 4 = 45.

Figure 5.   Odds ratios for the association between change in cerebrospinal fluid (CSF) human immunodeficiency virus (HIV) risk score and detectable CSF HIV RNA, Central Nervous System Human Immunodeficiency Virus Antiretroviral Therapy Effects Research (CHARTER) cohort at study entry, 2004–2007, (n = 811). Odds ratios and 95% confidence intervals per 1-, 5-, and 10-point increments in the CSF HIV risk score.

depression may also reduce the probability of having a detectable level of CSF HIV RNA.

Race was identified as a nonmodifiable correlate of detectable CSF HIV RNA, with blacks and Hispanics displaying significantly higher risk. Higher risk of HIV/AIDS acquisition has been associated with being black or Hispanic (43). Reasons for racial HIV disparities are complex and include differences in access to care and utilization of cART, differences in clinical response to cART, and proposed genetic variations including the *CCR5* (chemokine (C-C motif) receptor 5) and *CCL3* (chemokine (C-C motif) ligand 3) genes (44–46). Application of knowledge about the overall risk of detectable CSF HIV RNA may help addresses these disparities.

We present the CSF HIV risk score as a clinical tool to help improve the medical management of HIV. However, its utility may extend beyond the goal of suppressing HIV replication and apply to managing HAND. A recent algorithm for early detection of HAND identified age, current CD4 cell count, past CNS HIV-related diseases, and current cART duration as predictors (47). The CSF HIV risk score may allow research into how CSF HIV RNA, a proximal factor in the causal pathway to developing HAND, may affect HIV outcomes.

The CSF HIV risk score may offer insight into longitudinal cognitive changes when applied to already available and prospective epidemiologic data. It is conceivable that repeated monitoring of the CSF HIV risk score to ensure that low scores are maintained will lead to better neurocognitive and neuropsychiatric HIV outcomes. We caution, however, against the use of the risk score as a surrogate endpoint in clinical trials. This score may help identify patients for whom CSF examinations might be most informative.

A limitation to the use of this risk score is that depression was assessed by DSM-IV criteria. These criteria for depression may not be readily available to HIV care providers. In our population, persons who were depressed according to DSM-IV criteria had a mean Beck Depression Inventory II score of 25.0 (SD, 10.8). We did not evaluate the effect of current substance and alcohol use disorders because diagnoses of current DSM-IV substance and alcohol use disorders were infrequent, occurring in 0.9% and 0.8% of the population, respectively.

In this analysis, we were able to ascertain a temporal relationship between cART use and detectable CSF HIV. The type and duration of cART use was determined from patient medical records at the time of enrollment and were unlikely to be misclassified. Our study design also enhances the use of the risk score as a tool to make an assessment of current cART at the time of evaluation, which, in essence, is the utility of prognostic and diagnostic models. In the future, the risk predicted by the CSF HIV risk score needs to be compared with observed risks in another population for external validation. Its use in other populations may require calibration.

Strengths of this study include the large sample size of patients with CSF HIV RNA measurements. Approximately 15% of the study population had detectable CSF HIV RNA. The use of augmented multiple imputations allowed us to use data from the entire study cohort. The low ratio of retained potential predictors to number of outcomes, 1:26, ensured a good model fit with only 6.3% of fit due to noise, thereby reducing overoptimism in its application in other populations.

In conclusion, the CSF HIV risk score represents an advance in HIV management and monitoring of the CNS effects of HIV, providing a potentially useful tool for clinicians. Continuous CSF HIV risk score monitoring with the necessary physician actions, may help prevent HIV-related neurological and psychiatric complications and improve HIV outcomes.

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APPENDIX 1

Appendix Table 1. Central Nervous System Penetration Effectiveness Rankings of Frequently Used Antiretroviral Regimen (10)

Antiretroviral Class	Central Nervous System Penetration Effectiveness Ranking[a]			
	4	3	2	1
Nucleoside analogue reverse transcriptase inhibitors	Zidovudine	Abacavir	Didanosine	Tenofovir
		Emtricitabine	Lamivudine	Zalcitabine
			Stavudine	
Nonnucleoside analogue reverse transcriptase inhibitors	Nevirapine	Delavirdine	Etravirine	
		Efavirenz		
Protease inhibitors	Indinavir/ritonavir	Darunavir/ritonavir	Atazanavir	Nelfinavir
		Fosamprenavir/ritonavir	Atazanavir/ritonavir	Ritonavir
		Indinavir	Fosamprenavir	Saquinavir
		Lopinavir/ritonavir		Saquinavir/ritonavir
				Tipranavir/ritonavir
Entry/fusion inhibitors		Maraviroc		Enfuvirtide
Integrase strand transfer inhibitors		Raltegravir		

[a] Higher rankings reflect better central nervous system penetration estimates.

APPENDIX 2

Sensitivity analyses

We conducted a sensitivity analysis by developing the cerebrospinal fluid (CSF) human immunodeficiency virus (HIV) risk score using only the 790 participants with complete data (i.e., complete case analysis). The same set of potential predictors was retained as with the multiple imputation approach except "duration of current combination antiretroviral therapy (cART)." We forced "duration of current cART" in the final regression model under the assumption that therapeutic levels of cART need to be attained prior to objective assessment of effectiveness in reducing plasma and CSF HIV RNA. The observed associations and regression coefficients were similar for multiple imputations as with complete case analysis. In comparison, multiple imputation analysis yielded more precise estimates.