Validation of a Risk Score for HIV Acquisition in Young African Women with FACTS 001

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1 BACKGROUND

Adolescent girls and young women (AGYW) in South Africa continue to be disproportionally infected by HIV compared to same age males. Oral PrEP is recommended by WHO for populations at substantial risk for HIV infection (≥ 3% per year) and has the potential to reduce HIV infection in AGYW (1). Questions remain about how to identify AGYW who are at substantial risk for infection. Balkus *et al.* have published a risk score derived from women who participated in the VOICE trial (2). We sought to validate this score in a population of young South African women who participated in the FACTS trial to determine the utility of a risk score for PrEP programmes in our setting.

2 METHODS

- We used data from FACTS 001, a phase III, randomized, double-blind, placebo-controlled trial that followed 2,059 sexually active HIV negative women, 18-30 years-old at 9 South African sites between 2011 and 2014, to assess whether 1% tenofovir gel could reduce HIV acquisition (incidence=4.38%, CI: 3.79, 5.19).
- Total risk scores were generated for each participant by summing their scores on individual predictor items – using participant baseline data for the 7 risk score factors (Figure 1). One item from this score, detection of a curable STI at baseline, was not collected in FACTS, instead, we used self-report of any STIs over a participant's lifetime as a proxy.

Figure 1: African Women Full Risk Score (derived by Balkus *et al.* in VOICE) (2).

Predictor Items			
Age	less than 25	2	
	25 or older	0	
Living with partner	yes	0	
	no	2	
Alcohol use in the last three months	yes	1	
	no	0	
Partner provides financial support	yes	0	
	no	1	
Partner has other partners	yes	2	
	no	0	
	don't know	2	
Curable STI	yes	1	
	no	0	
HSV-2 positive	yes	2	
	no	0	
TOTAL			/11

- Score performance was assessed by (1) generating the HIV incidence per 100 person years in each risk score category; (2) calculating area under the receiver operating curve (AUC); (3) sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) at score cut-offs of ≥3 and ≥5.
- The unadjusted and adjusted effects of the 7 risk score items included in the score, as well as others of interest, were evaluated using Cox Proportional hazards for their association with HIV acquisition over 2.2 years of follow-up.

3 RESULTS

- 1,115 (54%) participants had complete data for all 7 risk score items. The majority of missing data was due to incomplete collection of the "partner exclusivity" item. Of these, 81 acquired HIV infections over 1876 person years of follow-up (incidence=4.32%, CI: 3.47, 5.37).
- Median age of the cohort was 23 years, IQR 20-25 years of age.

SCORE PERFORMANCE

- Scores of ≥3 identified 96% of the infections in 94% of the cohort, scores of ≥5 identified 84% of incident infections in 77% of the cohort (Table 1).
- All analyses were repeated at 1 year of follow-up, resulting in similar performance.

Table 1: HIV incidence and 95% confidence intervals by risk score category in FACTS (n=1,115).

Risk Score Value	FACTS 001		
	# of HIV infections	Total # of Women	HIV Incidence / 100 PY 95% CI
0	0	7	0
1	1	15	3.58 (0.50, 25.45)
2	2	50	2.51 (0.63, 10.03)
3	3	89	1.97 (0.63, 6.10)
4	7	90	4.68 (2.23, 9.81)
5	16	259	3.64 (2.23, 5.94)
6	13	138	5.62 (3.26, 9.67)
7	19	231	4.86 (3.10, 7.62)
8	9	123	4.26 (2.22, 8.19)
≥9	11	113	6.13 (3.40, 11.07)

Figure 2: AUC for the full risk score in validation (FACTS) cohort (n=1,115) = 0.56 (95% CI 0.50, 0.62).

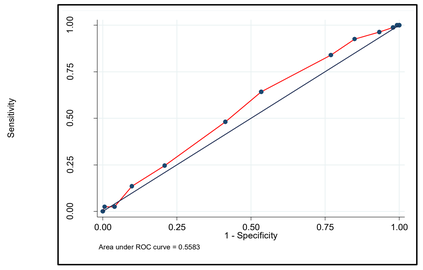
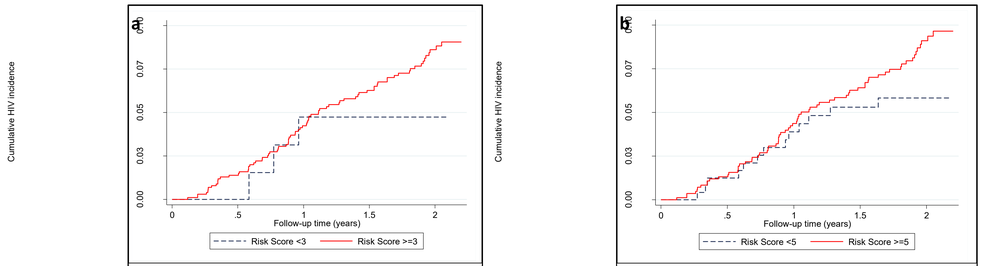


Figure 3: Cumulative HIV incidence over study time at risk score cut offs of a) ≥3 and b) ≥5 in validation (FACTS) cohort (n=1,115).



Sensitivity= 96%	PPV= 7%
Specificity= 7%	NPV=96%

Sensitivity= 84%	PPV= 8%
Specificity= 23%	NPV=95%

RISK FACTOR ANALYSIS

- In univariate analysis, 3 of the 7 risk factors included in the score, namely receiving financial support from partner (HR=1.67, 95% CI 1.02, 2.78), living with someone other than a partner (HR=1.93, CI 1.03, 3.6), and being HSV-2 positive (HR= 1.55, CI 1.10, 2.19), were found to independently increase a participant's risk of HIV acquisition (p-value <0.05).
- Among other factors of interest, those who reported their sexual behavior to be more risky than average in the past 28 days had 1.89 times (CI: 1.02, 2.77) greater risk of becoming HIV positive. Women who reported knowing their partner's HIV status and whose partners knew their HIV status were 0.60 (CI: 0.37, 0.97) and 0.31 (CI: 0.31, 0.71) times less likely to acquire HIV, respectively.
- In a multivariate model including all 7 risk score factors (Table 2), having a source of income independent of a partner was protective against HIV acquisition, while living with someone other than a partner was associated with a higher risk of HIV infection.

Table 2: African Women Full Risk Score multivariate model of risk factors for HIV acquisition in FACTS, stratified by site (n=1,115).

Predictors		aHR (95% CI)	p-value
Age	≥25 (Ref)	1	
	<25	0.89 (0.55, 1.46)	0.66
Living with	Partner (Ref)	1	
	Other	2.48 (1.13, 5.45)	0.02
Alcohol use last 3 months	No (Ref)	1	
	Yes	1.24 (0.72, 2.14)	0.43
Income source	Partner (Ref)	1	
	Other	0.50 (0.26, 0.99)	0.05
Partner has other partners	No (Ref)	1	
	Don't Know	1.41 (0.79, 2.53)	0.24
	Yes	0.76 (0.41, 1.42)	0.39
Ever had curable STI	No (Ref)	1	
	Yes	1.06 (0.65, 1.72)	0.81
HSV-2 positive	No (Ref)	1	
	Yes	1.41 (0.89, 2.23)	0.14

4 DISCUSSION

We found that in this entirely young South African population, the risk score did not differentiate sufficiently between women who were at substantial risk of HIV infection and those at lower risk. This tool had low discriminative ability in FACTS 001 (AUC: 0.56) compared to previous validations which included non-South African populations: VOICE (0.71), HPTN 035 (0.70), FEM-PrEP (0.58), and ASPIRE (0.66) (2,3). Furthermore, scores of ≥5 in VOICE identified 91% of infections among only 64% of the women, and had higher sensitivity and specificity than in FACTS (2).

Possible reasons for this include the younger age of the cohort, relative to previous trial cohorts. With a median age of 23 years, risk was uniformly high in this population. Unlike the cohorts in which the risk score was developed, the FACTS 001 trial population was wholly South African. Importantly, only 2/7 risk score items were found to predict HIV infection in multivariate analyses suggesting that other unmeasured factors are driving HIV risk in this population. Most notably, financial independence from a partner was protective in FACTS participants (aHR=0.50), in contrast to the VOICE trial population from where the score was derived (aHR=1.38) (2). This may reflect the role of transactional sex in shaping risk in young populations, in contrast to marriage which may be protective in older populations (4).

We recognize the limitations of our analysis. First, information on partner exclusivity was only collected in 54% of the sample and therefore the sample size available for analysis was greatly reduced. Second, we used self-report of an STI over a participant's lifetime as a proxy measure for detection of a curable STI at baseline. Lastly, although we looked at individual factors to investigate better predictors of HIV in this population we did not develop a new score from them.

CONCLUSION

Further validation of this risk score tool where all 7 items have been sufficiently collected in a younger population should be considered. Additionally, risk scores should be interpreted with care and one tool may not fit all populations. For example, there may be a need in young populations with high incidence for a robust tool that includes other variables, such as intimate partner violence. In lieu of consensus on risk factors or better measures, it may be appropriate to frame an individual's risk within their prevention product preferences, their ability to adhere, and the feasibility for each country to implement a range of products.

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