Validating the World Health Organization HIV Drug Resistance Early Warning Indicators

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Background

- In 2006, the WHO released the HIV Drug Resistance (HIVDR) Early Warning Indicator (EWI) Monitoring system as a part of the WHO Global Strategy for the Surveillance and Monitoring of HIVDR.
- EWIs measure ART site factors associated with HIVDR prevention, without the use of HIVDR laboratory testing.
- However, there is a dearth of published studies validating EWIs. Thus, we validated the WHO EWIs (from the April 2010 update) using data from British Columbia, Canada, a high-income setting with universal access to HIV treatment and routine HIV laboratory and resistance.

Methods

- Eligible individuals were ART-naïve, ≥19 years old, initiated ART between January 1st, 2000-December 31st, 2012, had ≥15 months of follow-up post-ART initiation, and were without baseline transmitted HIVDR. Individuals were followed for acquired HIVDR until March 31st, 2014, the last contact date, or death.
- We tested the associations between acquired HIVDR and EWIs 1, 2, 3a, 3b, 4b, 7b, and 8. Also, we created a variable called the EWI Score which is the number of EWIs an individual failed to meet the targets of categorized as 0, 1, 2, 3, and ≥4. The EWI Score includes EWIs 2-8.
- We built multivariable logistic regression models to explore associations between the EWI Score and acquiring: i) any class of HIVDR (either a non-nucleoside reverse-transcriptase inhibitor (NNRTI), 3TC/FTC, any other nucleoside reverse-transcriptase inhibitor (NRTI), or protease inhibitor (PI) resistance), ii) NNRTI, and iii) 3TC/FTC resistance, during follow-up. Also, predictive models were built to assess whether the EWI Score and individual EWIs predicted acquiring any class of HIVDR (yes/no).
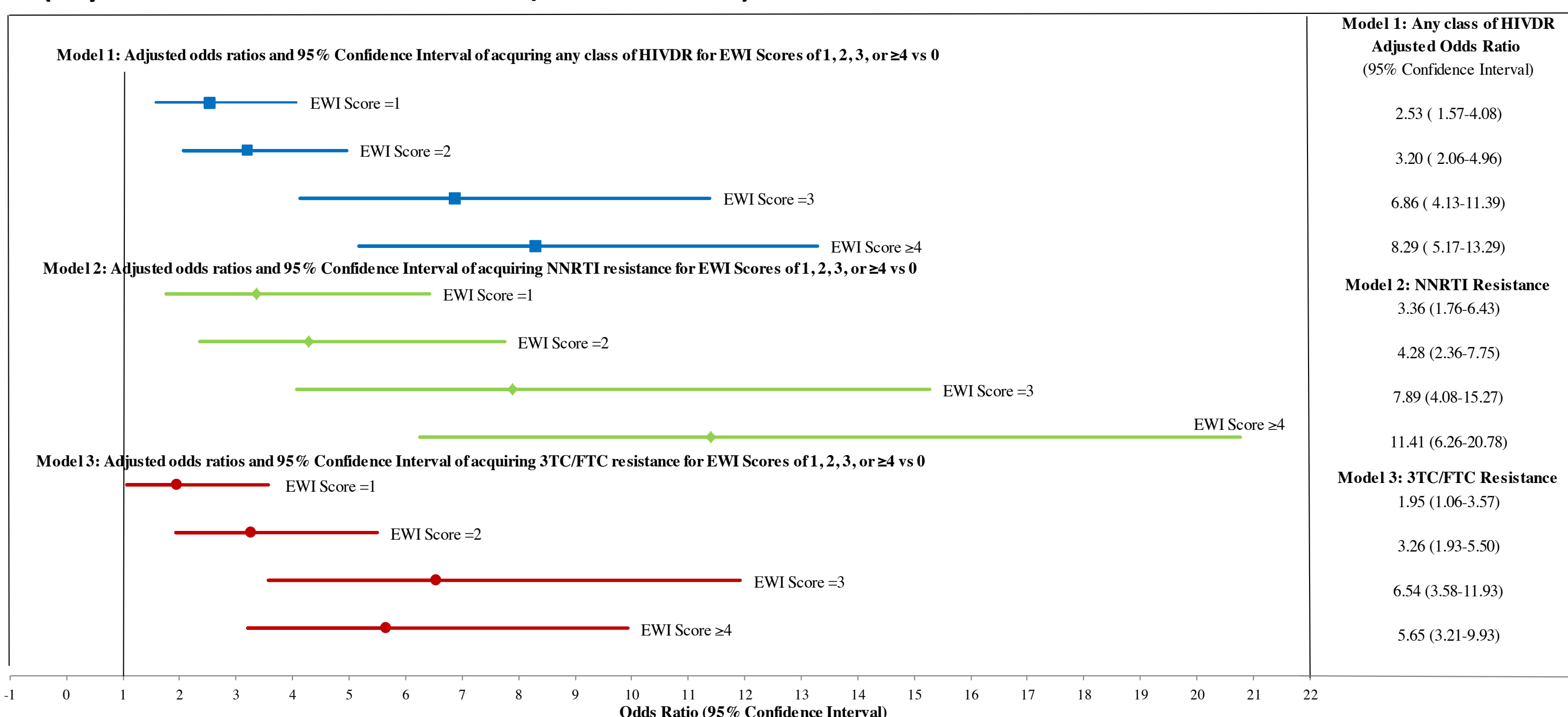
Results

- We included 3,082 individuals (82% males, median age: 42 years (25th –75th percentile: 34-49) in our analysis.
- All explored EWIs, except for EWI 1 were associated with having any class of HIVDR or a NNRTI resistance during follow-up. Also, all EWIs except for EWIs 1&2 were associated with a 3TC/FTC or any other NRTI resistance (Table 1).
- The adjusted odds ratio for acquiring any class of HIVDR resistance for an EWI Score≥4 (worst score) versus 0 (best score) was 8.29 (95%CI 5.17–13.29) (Figure 1); predictive model concordance index=0.848. Predictive models for meeting the targets of individual EWIs, obtained similar concordance indexes of 0.850, 0.857, 0.852, 0.859, 0.866, and 0.866 for EWI1, EWI2, EWI3a, EWI3b, EWI4b, EWI7b, and EWI8, respectively.

Table 1. WHO EWIs and baseline characteristics associated with developing HIVDR during follow-up.

EWI	EWI Description	EWI Criteria Met	Site Target Met N (%)	Any Class of HIVDR			3TC/FTC			NNRTI			NRTI			PI		
				No	Yes	P	No	Yes	P	No	Yes	P	No	Yes	P	No	Yes	P
1	ART prescribing practices	Yes	92%	2556 (91)	267 (9)	0.5820	2662 (94)	161 (6)	0.7780	2661 (94)	162 (6)	0.5780	2756 (98)	67 (2)	0.6720	2803 (99)	20 (1)	0.1370
		No	8%	232 (89)	27 (11)		246 (5)	13 (5)		242 (93)	17 (7)		252 (97)	7 (3)		255 (98)	4 (2)	
2	Patients lost to follow-up 12 months after ART initiation	Yes	87%	2336 (91)	218 (9)	<0.0001	2409 (94)	145 (6)	0.5600	2425 (95)	129 (5)	0.2130	2496 (98)	58 (2)		2535 (99)	19 (1)	0.2370
		No	13%	324 (83)	66 (17)	<0.0001	365 (94)	25 (6)	<0.0001	346 (89)	44 (11)	<0.0001	377 (97)	13 (3)	<0.0001	385 (99)	5 (1)	0.0890
3a	Patients on appropriate first-line ART 12 months after ART initiation	Yes	77%	2169 (92)	176 (8)		2235 (95)	110 (5)		2238 (95)	107 (5)		2303 (98)	42 (2)		2330 (99)	15 (1)	
		No	23%	575 (84)	113 (16)	<0.0001	626 (91)	62 (9)	<0.0001	620 (90)	68 (10)	<0.0001	657 (95)	31 (5)	<0.0001	679 (99)	9 (1)	1.0000
3b	Patients who changed ART regimen during the first 12 months to a regimen that includes a different drug class	Yes	84%	2360 (92)	194 (8)		2441 (96)	113 (4)		2449 (96)	105 (4)		2509 (98)	45 (2)		2533 (99)	21 (1)	
		No	16%	384 (80)	95 (20)	<0.0001	420 (88)	59 (12)	<0.0001	409 (85)	70 (15)	<0.0001	451 (94)	28 (6)	0.0040	476 (99)	3 (1)	0.2400
4b	On-time ARV drug pick-up	Yes	74%	2123 (94)	145 (6)		2185 (96)	83 (4)		2187 (96)	81 (4)		2225 (98)	43 (2)		2253 (99)	15 (1)	
		No	26%	647 (81)	147 (19)	<0.0001	704 (89)	90 (11)	<0.0001	696 (88)	98 (12)	<0.0001	764 (96)	30 (4)	<0.0001	785 (99)	9 (1)	0.0480
7b	Adherence to ART	Yes	67%	1941 (95)	110 (5)		1981 (96)	70 (4)		1991 (97)	60 (3)		2018 (98)	33 (2)		2040 (99)	11 (1)	
		No	33%	847 (82)	184 (18)	<0.0001	927 (90)	104 (10)	<0.0001	912 (88)	119 (12)	<0.0001	990 (96)	41 (4)	<0.0001	1018 (99)	13 (1)	<0.0001
8	VL suppression 12 months after ART initiation	Yes	89%	2313 (93)	165 (7)		2382 (96)	96 (4)		2383 (96)	95 (4)		2441 (99)	37 (2)		2465 (99)	13 (1)	
		No	11%	198 (68)	95 (32)	<0.0001	232 (79)	61 (21)	0.0240	228 (78)	65 (22)	<0.0001	266 (91)	27 (9)	0.0950	285 (97)	8 (3)	0.7900
Sex, n (%)																		
	Female			485 (86)	78 (14)		520 (92)	43 (8)		512 (91)	51 (9)		544 (97)	19 (3)		558 (99)	5 (1)	
	Male			2303 (91)	216 (9)	<0.0001	2388 (95)	131 (5)	<0.0001	2391 (95)	128 (5)	<0.0001	2464 (98)	55 (2)	0.0110	2500 (99)	19 (1)	<0.0001
HIV risk category, n (%)																		
	MSM			518 (93)	41 (7)		534 (96)	25 (4)		535 (96)	24 (4)		542 (97)	17 (3)		555 (99)	4 (1)	
	PWID			559 (84)	108 (16)		611 (92)	56 (8)		590 (88)	77 (12)		645 (97)	22 (3)		658 (99)	9 (1)	
	Heterosexual			186 (89)	24 (11)		192 (91)	18 (9)		199 (95)	11 (5)		205 (98)	5 (2)		208 (99)	2 (1)	
	Other			429 (85)	74 (15)		457 (91)	46 (9)		461 (92)	42 (8)		486 (97)	17 (3)		495 (98)	8 (2)	
	Unknown			1096 (96)	47 (4)	<0.0001	1114 (98)	29 (2)	<0.0001	1118 (98)	25 (2)	<0.0001	1130 (99)	13 (1)	<0.0001	1142 (100)	1 (0)	<0.0001
Baseline CD4 cell count, n (%)																		
	< 200 cells/mm³			1030 (84)	199 (16)		1097 (89)	132 (11)		1113 (91)	116 (9)		1173 (95)	56 (5)		1209 (98)	20 (1)	
	200 − 350 cells/mm³			914 (93)	66 (7)		948 (97)	32 (3)		935 (95)	45 (5)		967 (99)	13 (1)		977 (100)	3 (0)	
	≥350 cells/mm³			827 (97)	28 (3)		845 (99)	10 (1)		838 (98)	17 (2)		850 (99)	5 (1)		854 (100)	1 (0)	
Age at baseline (years)																		
	Median (25-75th percentile)			42 (34,49)	39.56 (34,46)	0.0040	42 (34,49)	39 (35,46)	0.0260	42 (34,49)	38 (32,44)	<0.0001	42 (34,46)	40 (34,46)	0.1230	42 (34,49)	42 (36,47)	0.9100
Log 10 baseline viral load (copies/mL)																		
	Median (25-75th percentile)			4.80 (4.30,5.00)	5.00 (4.70,5.00)	<0.0001	4.83 (4.30,5.00)	5.00 (4.90,5.00)	<0.0001	4.84 (4.30,5.00)	5.00 (4.60,5.00)	<0.0001	4.85 (4.30,5.00)	5.00 (4.60,5.00)	<0.0001	4.85 (4.30,5.00)	5.00 (4.20,5.00)	0.1700

Figure 1. Adjusted odds ratios relating the Early Warning Indicator (EWI) Score (categorized as 0, 1, 2, 3, ≥4) with acquired HIV drug resistance (any class of HIVDR or NNRTI or 3TC/FTC resistance).

Note: Results from three multivariable logistic regression models relating the EWI Score to either: i) any class of HIVDR, ii) a NNRTI resistance, and iii) a 3TC/FTC resistance. Multivariable models were adjusted for the baseline covariates age, CD4 cell count, viral load, and study follow-up time. Follow-up time=first resistance date (of either any HIVDR or NNRTI or 3TC/FTC)–first ARV date.

Conclusion

- Several EWIs were found to be associated with and predictive of HIVDR. Also, failing to meet the target of ≥1 EWI was predictive of acquiring any class of HIVDR. Similar analyses should be performed to validate the most recently published WHO EWIs using data from low- and middle-income settings on a site-level.