Integrase Inhibitor Exposure is Linked to Neurocognitive Deficits in HIV

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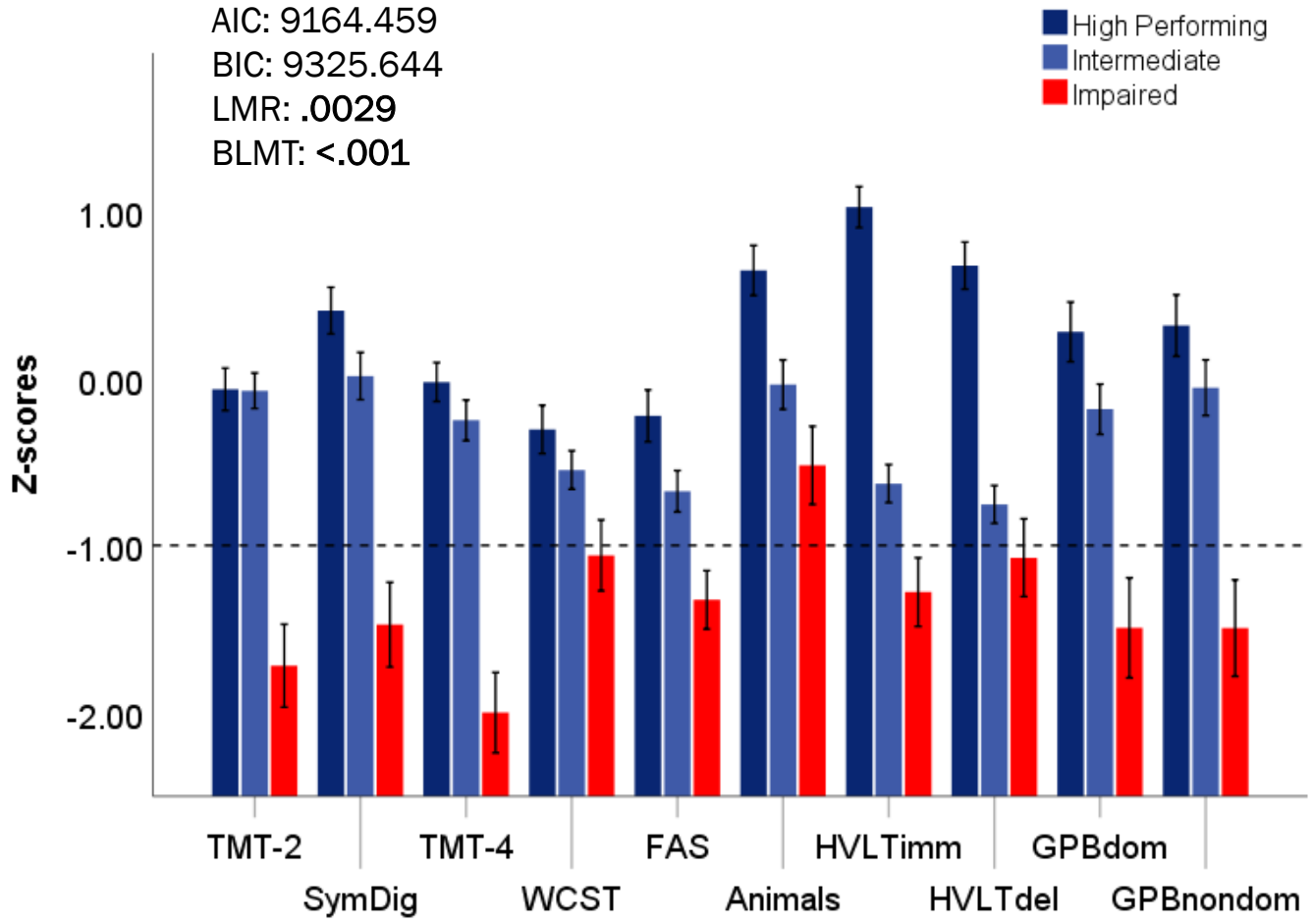
Background: Despite the availability of modern antiretroviral therapy (ART), neurocognitive impairment persists among some persons with HIV (PWH). We investigated the role of exposure to four major classes of ARTs in neurocognitive impairment in PWH.

Methods: A single-site cohort of 343 PWH was recruited. Lifetime ART medication history was obtained from medical health records. We evaluated the role of ART exposure as predictor of neurocognitive impairment using univariate analyses and machine learning, while accounting for potential effects of demographic, clinical, and comorbidity-related risk factors.

Results: Three neurocognitive profiles were identified, one of which showed neurocognitive impairment (Figure 1). Out of a total of 26 tested variables, two random forest analyses identified the most important characteristics of the neurocognitively impaired group (N=59): Compared to a neurocognitively high performing group (N=132; F1-score=0.79), we uncovered 13 important risk factors (Figure 2); compared to an intermediately performing group (N=152; F1-score=0.75), 16 risk factors emerged (Figure 3). Longer lifetime ART-exposure, especially to integrase inhibitors, was one of the most important predictors of neurocognitive impairment in both analyses (rank 2 of 13 and rank 4 of 16, respectively), superseding effects of age (rank 11/13, rank 15/16) and HIV duration (rank 13/13, rank 16/16). Concerning specific integrase inhibitors, the impaired group had significantly longer dolutegravir exposure (p=.011) compared to the high performing group (p=.012; trend compared to the intermediate group p = 0.063).

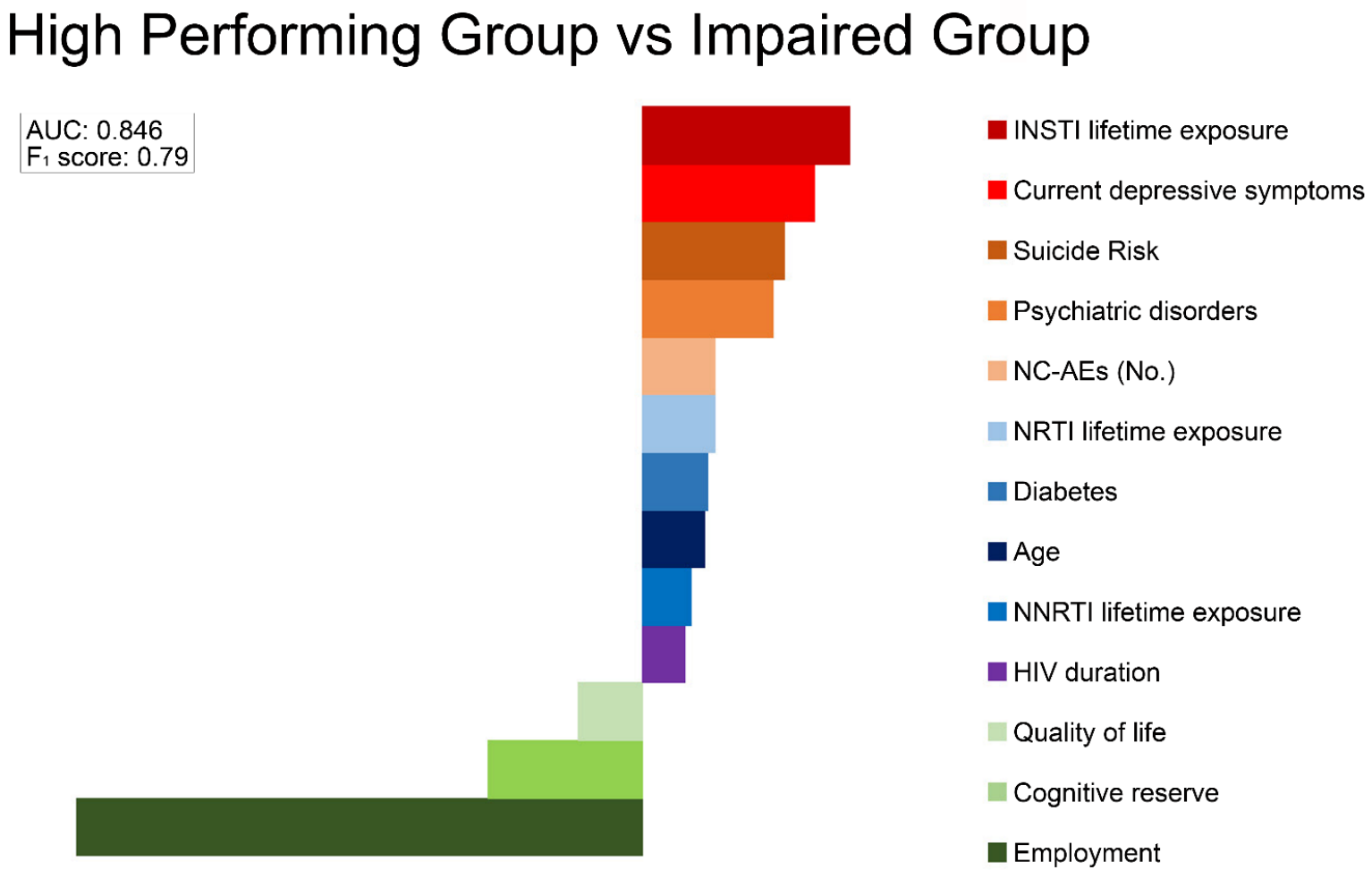
Conclusion: A longer duration to integrase inhibitor intake was negatively related to cognition in this cohort. Our findings suggest that possible cognitive complications of long-term exposure to integrase inhibitors, in particular dolutegravir, should be closely monitored in PWH.

Figure 1: Latent Profile Analyses of 343 HIV-infected participants from the Southern Alberta HIV clinic. Bars represents average performance (Z-score) in 10 individual neuropsychological tests.



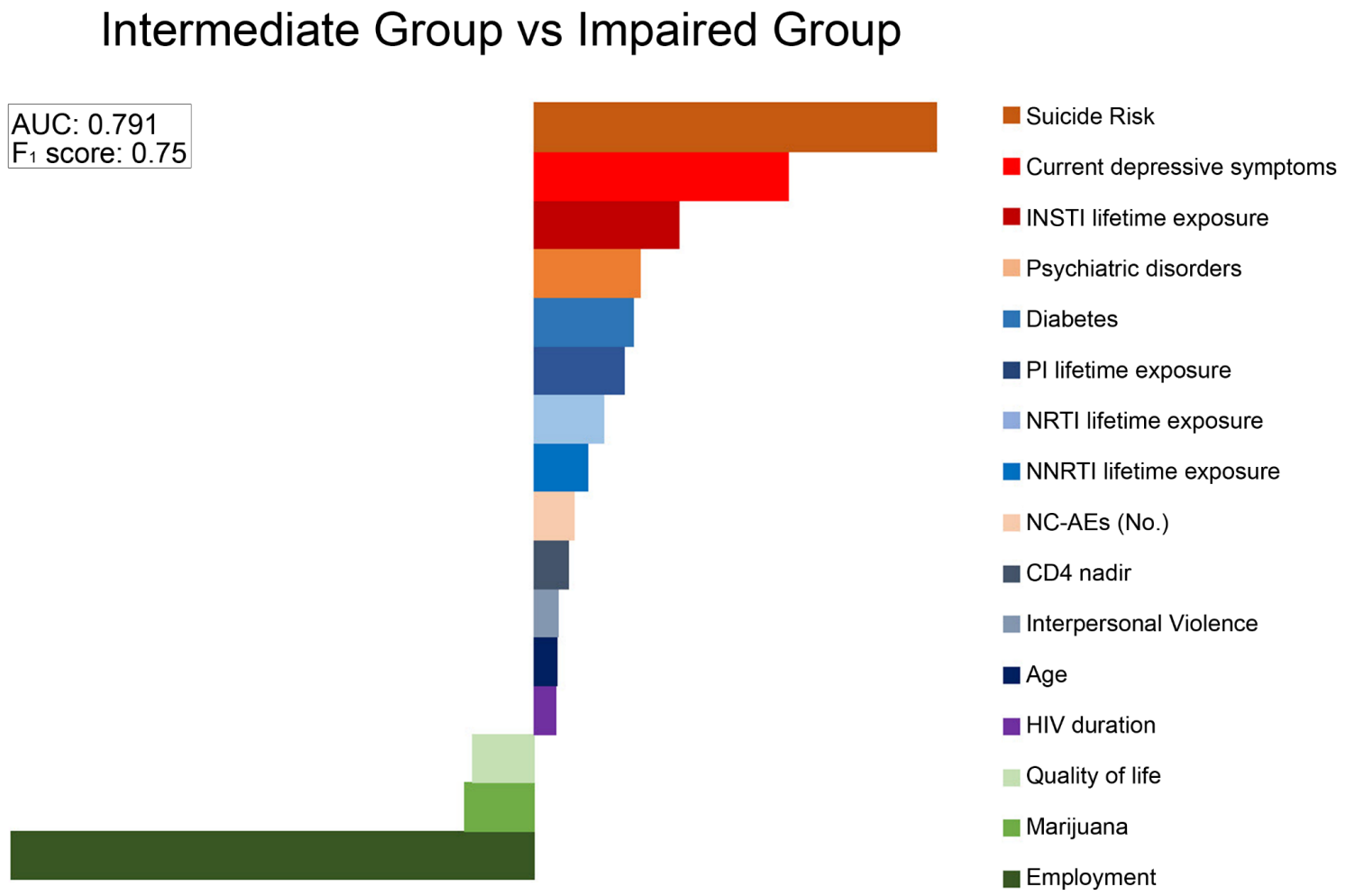
Abbreviations. Animals: Delis-Kaplan Executive Function System Category Fluency (animals), FAS: Delis-Kaplan Executive Function System Letter Fluency, GPBdom.: Grooved Pegboard (dominant hand), GPBnondom.: Grooved Pegboard (non-dominant)., HVLT del.: Hopkins Verbal Learning Test (delayed), HVLT imm.: Hopkins Verbal Learning Test (immediate), SDMT: Symbol Digit Modalities Test, TMT-2: Trail Making Test 2, TMT-4: Trial Making Test 4, WCST: Wisconsin Card Sorting Test 64-Card version

Figure 2: Random Forest Analysis comparing groups with high versus impaired neurocognitive performance. Direction of the bars corresponds placement into each group. The magnitude of bars corresponds to the variable importance values in the analysis.



Abbreviations. INSTI: integrase inhibitor, NC-AE: non-ART medications with known neurocognitively adverse effects, NNRTI: non- nucleoside reverse transcriptase inhibitor, NRTI: nucleoside reverse transcriptase inhibitor, PI: protease inhibitor

Figure 3: Random Forest Analysis comparing groups with high versus impaired neurocognitive performance. Direction of the bars corresponds placement into each group. The magnitude of bars corresponds to the variable importance values in the analysis.



Abbreviations. See Figure 2