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Neurocognitive Impairment Risk Among Individuals With Multiple Drug-Resistant Tuberculosis and Human Immunodeficiency Virus Coinfection: Implications for Systematic Linkage to and Retention of Care in Tuberculosis/ Human Immunodeficiency Virus Treatment

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Abstract

Although neurocognitive impairment (NCI) is a well-recognized challenge in HIV, there is little evidence regarding it among individuals with multiple drug-resistant tuberculosis (MDR-TB) within HIV endemic sub-Saharan Africa. The extent of NCI risk, particularly HIV-associated neurocognitive disorders (HAND) risk, was investigated in 200 microbiologically confirmed MDR-TB inpatients at a TB-specialist hospital in KwaZulu-Natal Province, South Africa. Within this population, the prevalence of HIV co-infection, major depressive episode and substance use disorder (SUD) was 89.50%, 10.50% and 7.00% respectively. After excluding individuals with major depressive episode/substance use disorder and mono-infection (i.e. MDR-TB without HIV), the prevalence of HAND risk was 43.5%. Older and low-income individuals had significantly greater odds of HAND risk, while those with family members/relatives who work(ed) in the health services had lower odds. The role of timely linkage to and retention of care in TB/HIV treatment to offset cognitive decline in MDR-TB/HIV co-infected individuals needs to be investigated further.

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Keywords

MDR-TB; HIV; neurocognitive impairment; South Africa

Introduction

The rapid scale-up of antiretroviral therapy (ART) has resulted in substantial population-level reductions in HIV acquisition risk (Tanser et al., 2013), and has improved life expectancy in South Africa (Bor et al., 2013). Despite considerable progress in stabilizing the HIV epidemic, the incidence remains unacceptably high, accompanied (and complicated) by persistent TB challenges. In particular, KwaZulu-Natal (KZN) Province is home to the confluence of the multi-drug resistant TB (MDR-TB) and HIV epidemics, with strict adherence to medication being key to sustained viral suppression (Gardner et al., 2008; O'Connor et al., 2013; Kulkarni et al., 2013). However, as a recent large treatment-as-prevention population-based trial in KZN revealed, linkage to care, and subsequent ART adherence in community settings, remain serious challenges (Iwuji et al., 2018). Despite countless investigations that document neurocognitive problems to be associated both with HIV (Reger et al., 2002; Clifford and Ances, 2013; Clifford, 2017; Ciccarelli et al., 2011) and adherence to ART (Becker et al., 2011; Albert et al., 1999; Hinkin et al., 2002; Durvasula et al., 2001), to our knowledge, no research on the extent of neurocognitive impairment (NCI) risk in the MDR-TB population in sub-Saharan Africa has been conducted; this is in spite of a high rate of HIV co-infection. The current study aimed to address this important evidence gap by documenting the extent of NCI risks, particularly HIV-associated neurocognitive disorders (HAND) risk, and possible contributing factors, among individuals with MDR-TB and HIV.

Methods

Study design and participants

We prospectively enrolled in-patients with microbiologically confirmed MDR-TB who were admitted to a referral-based TB-specialist hospital in KwaZulu-Natal (KZN) Province from September 2015 through October 2016. The overall inclusion criteria were: consenting individuals between 21 and 59 years with no prior history of MDR-TB treatment. Individuals without primary school education were excluded, due to the participants being required to have basic literacy to participate in the assessment. For this current investigation, we excluded individuals with major depressive and substance use disorders, as suggested by Joska et al. (2016), and similar to a previous study (Singh et al., 2010). Furthermore, as the focus of our current investigation was HIV-associated neurocognitive disorders risk, we excluded individuals without HIV. All standardized questionnaires and assessment instruments were translated into isiZulu (a local language in KZN) based on a translation/back-translation process. All assessments were administered in English or isiZulu by Master's-level clinical psychologists who received training under the supervision of a senior clinical psychologist. Written informed consent was obtained from each study participant, and ethical approval obtained from the University of KwaZulu-Natal's Biomedical Research Ethics Committee (BF251/14).

Measures

The outcome of the study was HIV-associated neurocognitive disorders (HAND) risk, which was assessed using the International HIV Dementia Scale (IHDS). The instrument is brief, easily administered by non-neurologists, and culturally neutral (given its nonrestrictive language requirements), making it suitable for resource-limited settings (Sacktor et al., 2005); with a systematic review (Zipursky et al., 2013) and meta-analysis (Hu et al., 2012) confirming its relatively high diagnostic performance accuracy for detecting HAND risk in such contexts. The IHDS consists of three neurocognitive function domain screening parts: motor speed, psychomotor speed and memory, and has been used in other sub-Saharan studies to identify HIV-associated neurocognitive disorders risk (Sacktor et al., 2005; Njamnshi et al., 2008; Holguin et al., 2011; Nakasujja et al., 2010). The final IHDS score is based on a total of the three sub-scores (total score ranging from 0–12 points), with the internationally recommended cut-off threshold for confirmed HAND risk being a total IHDS score of 10 points. The instrument has been demonstrated to have fair/good diagnostic classification function within the South African setting to identify individuals at HAND risk (Joska et al., 2016).

The MDE (i.e., major depression) and substance use disorder (encompassing substance abuse and dependence) current episode was diagnosed using the Mini International Neuropsychiatric Interview (MINI) v6.0 (Sheehan et al., 1998), a structured diagnostic schedule utilizing DSM-IV criteria. Research assistants underwent training for MINI that was conducted by a South African psychiatrist. Information on HIV status was obtained from the National Health Laboratory Service that was situated at the study site. The infection status of MDR-TB participants was classified as ‘co-infection’ (with HIV) and ‘mono-infection’ (without HIV) respectively. Information on socio-demographic background was obtained through a face-to-face standardized/structured interview. An exploratory question on the potential role of family networks for linkage to care and health literacy was included in the structured socio-demographic questionnaire; namely, participants were asked if they had family members/relatives who work(ed) in the health services.

Data analysis

The analysis consisted of two components. First, descriptive statistics summarized the socio-demographic and clinical characteristics of participants with MDR-TB, both before and after excluding people who were HIV-negative and/or had major depression/substance use disorders. Second, adjusted logistic regression models were used to identify the socio-demographic correlates of HAND risk, after applying the same exclusion criteria as above. We tested for potential multi-collinearity for using a variance inflation factor (VIF); and assessed the overall goodness-of-fit (Hosmer, Lemeshow, and Sturdivant, 2013) of the fitted model based on the Hosmer-Lemeshow test (10 groups based on percentile ranks). A VIF exceeding five is often regarded as indicating the presence of considerable multicollinearity, and was applied in this study (Studenmund, 2014).

Results

Socio-demographic and clinical characteristics

The socio-demographic and clinical characteristics of MDR-TB participants before and after applying the exclusion criteria are presented in Table 1. Overall (N=200), the majority were female (n = 161; 80.50%), Black African (n = 196; 98.00%), and earning R1000 [\$78] per month (n = 119; 59.50%). The mean number of education years was 10.88 (SD=1.29). Approximately a third (n=60) had experienced a death in the family within the last 24 months, and 8.50% (n=17) had family/relatives who work(ed) in the health service. In terms of clinical characteristics, prevalence rates were: 89.50% (n=179) for HIV co-infection, 10.50% (n=21) for major depressive disorder (MDE), and 7.00% (n=14) for substance use disorder (SUD). The total study sample, after excluding those who had either mono-infection (i.e. MDR-TB without HIV) or major depression/substance use disorder, was 151.

Socio-demographic correlates of HAND risk

The prevalence of HAND risk was 43.5%, after excluding individuals with mono-infection and/or MDE/SUD. The results of the adjusted logistic regression analyses (Table 2) found that older (aOR=3.01, 95% CI: 1.01–8.93) and low-income (aOR=5.72, 95% CI: 1.29–25.45) study participants had greater odds of HAND risk. In contrast, individuals with family members/relatives who work(ed) in the health services, had lower odds of HAND risk (aOR=0.19, 95% CI: 0.04–0.98). No presence of considerable multi-collinearity was detected, as the VIF values of covariates in the fitted regression model ranged from 1.05–3.53 (mean = 1.62). Lastly, the Hosmer-Lemeshow test indicated an overall goodness-of-fit of the fitted model ($p=0.99$).

Discussion

This study is, to our knowledge, the first to investigate the extent of HAND risk among MDR-TB patients from sub-Saharan Africa in an HIV and TB endemic region. Our analysis also accounted for the important confounding role of major depression and substance use disorders in evaluating cognitive impairment in this population. Significantly higher HAND risk was identified among socially vulnerable individuals who were older and of low-income status. Conversely, having family members/relatives who work(ed) in the health services was protective against HAND risk, highlighting the importance of timely linkage to and retention of care in TB and HIV treatment among MDR-TB patients.

The absence of similar studies that are generalizable for MDR-TB sample populations makes comparisons difficult. Sub-Saharan studies that have utilized IHDS generally in Botswana (Lawler et al., 2010), Cameroon (Njamnshi et al., 2008; Njamnshi et al., 2009; Atashili et al., 2013), Malawi (Patel et al., 2010), Nigeria (Royal et al., 2012), South Africa (Joska et al., 2016) and Uganda (Kinyanda et al., 2011), suggest that HAND risk among individuals with HIV ranges from 14.0%–85.0%, which places our study rate (43.5%) in mid-range. As TB is often shown to exacerbate HIV disease progression (Mayer and Dukes Hamilton, 2010), which can negatively impact an immune response, a higher rate of HAND may have been expected, as most of our participants were co-infected with MDR-TB/HIV. It

is possible that the lower than expected rate of HAND risk in our sample may relate to the fact that our study participants were receiving intensive inpatient treatment for MDR-TB; although against this is the fact this sample was naive for MDR-TB specific treatment.

Our major limitations were the lack of reliable biomarker measures and information about medication that may influence HAND risk. First, as per the KZN Department of Health policy, our in-patients with HIV were immediately placed on ART on admission. While we acknowledge viral load and CD4 as potentially important predictors of NCI risk (Ellis et al., 2011), it has also been established that they no longer become significant indicators among ART-treated patients (Heaton et al., 2011). We acknowledge that viral load and CD4 measures are needed for future longitudinal investigations of HAND in community samples outside clinical settings.

Conclusion

Lessons have been learnt from the recent HIV treatment-as-prevention trial in KZN and other studies (Iwujii et al., 2018; Kay et al., 2016). The viability of Universal Test and Treat (UTT) strategies towards achieving the 90–90–90 UNAIDS goal (i.e. diagnose 90% of HIV-positive people, initiate 90% on ART, 90% of whom will be virally suppressed) (UNAIDS, 2014) in resource-limited settings, will depend on successfully addressing the difficult challenges of engaging high risk groups (e.g. MDR-TB/HIV co-infected) in the last two legs of the cascade of care (i.e. linkage to and retention of care). Adherence to ART, highly intertwined with NCI (Becker et al., 2011; Albert et al., 1999; Hinkin et al., 2002; Durvasula et al., 2001), must be sustained by systematic linkage to and retention of care. This is essential to reducing the unsuppressed viral load, which poses a serious threat for perpetuating the onward HIV transmission in generalized epidemic settings, such as South Africa.

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Table 1.

Sociodemographic and clinical characteristics of MDR-TB study participants

	Overall (n=200)		Final sample [‡] (n=151)	
	n	%	n	%
Gender:				
	161	80.50	128	84.77
	39	19.50	23	15.23
Age category:				
	65	32.50	48	31.79
	87	43.50	66	43.71
	48	24.00	37	24.50
Years of education:				
	Mean = 10.88	SD=1.29	Mean = 10.83	SD=1.31
Marital status:				
	113	56.50	84	55.63
	20	10.00	11	7.28
	67	33.50	56	37.09
Income:				
	119	59.50	89	58.94
	58	29.00	45	29.80
	23	11.50	17	11.26
Family death in the last 24 months:				
	139	69.85	98	65.33
	60	30.15	52	34.67
Presence of family/relatives who work(ed) in health service:				
	183	91.50	138	91.39
	17	8.50	13	8.61
Infection status:				
	21	10.50		
	179	89.50		
major depressive episode:				
	179	89.50		
	21	10.50		
Substance use disorder (SUD):				
	190	95.00		
	10	5.00		

[‡]Final sample after excluding major depressive episode, SUD and mono-infected individuals.

Table 2.

Adjusted logistic regression analysis results identifying potential risk and protective factors of HAND risk

		aOR	aOR (Std)	SE	95% CI	
Gender:	[Female]					
	Male	0.78	0.91	0.41	0.27	2.20
Age category:	[21–29]					
	30–39	0.81	0.90	0.34	0.35	1.86
	40+	3.01	1.60	1.67	1.01	8.93
Education:	Number of years	0.99	0.98	0.15	0.74	1.32
Marital status:	[No relationship/partner]					
	Married/Stable partner	1.41	1.19	0.55	0.65	3.04
	Casual partner	1.68	1.15	1.18	0.42	6.63
Income:	[R5001]					
	R1000	5.72	2.36	4.36	1.29	25.45
	R1001–R5000	2.49	1.52	1.91	0.55	11.24
Family death in the last 24 months:	[No]					
	Yes	0.92	0.96	0.35	0.44	1.94
Presence of family/relatives who work(ed) in health service:	[No]					
	Yes	0.19	0.62	0.16	0.04	0.98

HAND stands for HIV-associated neurocognitive disorders.

Std indicates standardized. SE and 95% CI based on aOR results.