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Prevalence of shingles and its association with PTSD among HIV-infected women in Rwanda

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ABSTRACT

Objective: To examine the prevalence of reported shingles in the last 6 months and its association with post-traumatic stress disorder (PTSD), depression and severity of HIV disease in Rwandan women with HIV.

Settings: This cross-sectional study was conducted as part of the Rwanda Women's Interassociation Study and Assessment (RWISA), an observational cohort study designed to assess the impact of HIV and residual factors from experiencing rape in the 1994 genocide in Rwandan women. Participants were recruited through grassroots women's associations of people living with HIV infection and clinical care sites for HIV infection. Most participants (58.5%, n=405/692) had PTSD.

Participants: This cross-sectional analysis was conducted in 710 HIV-infected women enrolled in RWISA. Inclusion criteria were: age >15 years, informed consent, HIV test, ability to complete the interview in the local language, travel to and from the research site and participate in a baseline outpatient visit, and being naive to antiretroviral therapy at enrolment.

Primary and secondary outcome measures: The outcome of interest was self-reported shingles in the past 6 months. The exposure was PTSD defined using the cross-culturally validated Harvard Trauma Questionnaire.

Results: Overall prevalence of reported shingles in the past 6 months was 12.5% (n=89/710). There was an inverse relationship between shingles prevalence and immunological status: 7.6%, 12.3% and 16.7% of women with CD4 >350, 200–350 and <200 cells/μL, respectively, reported singles (p=0.01). In multivariate analysis, PTSD (aOR 1.7; 95% CI 1.02 to 2.89) and low CD4 (aOR 2.4; 95% CI 1.23 to 4.81) were independently associated with reported shingles in the past 6 months.

Conclusions: Our study found a significant independent relationship between PTSD and reported shingles, suggesting that PTSD may be associated with immune compromise that can result in herpes zoster reactivation. Further study is needed. It also confirmed previous findings of a strong relationship between shingles and greater immunosuppression in women with HIV infection.

Strengths and limitations of this study

- The strength of this study lies in the HIV-infected study population in which an association of shingles and post-traumatic stress disorder (PTSD) was assessed for the first time.
- The outcome 'shingles in the past 6 months' limited the potential for recall bias for events in the distant past.
- The Harvard Trauma Questionnaire, a cross-culturally validated instrument measuring trauma and torture events and PTSD symptoms, was adapted to the Rwandan experience by experts in the field.
- Limitations are due to the cross-sectional design (potential recall bias, causality, generalisability).

INTRODUCTION

Shingles is a cutaneous disease caused by varicella (herpes) zoster, the virus that causes chickenpox in childhood.[1][2] Shingles can occur in any patient who has previously been infected with the varicella zoster virus after reactivation of virus that has remained latent within sensory neurons.[1][3–5] Older age and/or immune impairment from emotional stress, transplantation rejection suppressants, steroids, chemotherapy and HIV infection are some of the factors that may trigger shingles.[6–8] Although typically shingles is benign with pain, skin redness and vesicles along affected nerve roots, it can be associated with clinically significant cutaneous (persistent and severe rash), ophthalmic and neurological complications, or post-herpetic neuralgia.[2][9][10]

Several studies found strong positive associations between shingles and HIV infection with a higher incidence in those with greater HIV-induced immunological suppression.[11–16] Despite the strong association of HIV infection with shingles, studies have been inconsistent regarding the precise relationship between

shingles and CD4 cell count in HIV-infected persons, often finding shingles was equally likely to occur early and later in the course of HIV disease.[12 16–23]

There is still limited evidence for the impact of antiretroviral treatment (ART) on shingles occurrence, but some studies showed ART to be protective against shingles among HIV-infected adults.[24–26]

Other studies suggest that post-traumatic stress disorder (PTSD) and depression are both associated with high levels of systemic immune activation,[27 28] as is HIV infection.[29]

Given the strong link between PTSD, high levels of systemic immune activation and HIV through similar mechanisms, it is plausible that PTSD along with HIV could increase susceptibility to shingles. In addition, HIV-positive patients with PTSD may be at increased risk for adverse outcomes from comorbid medical conditions due to medication non-adherence being promoted by PTSD, and therefore reduced immunological capability.[30 31] Emotional stressors such as PTSD may enhance progression to HIV through several pathways such as central nervous system activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, both of which modulate the release of hormones which can lead to qualitative and quantitative changes in immune functioning.[12 32]

In a retrospective, case–control study of 101 healthy community-dwelling adults, high levels of stressful events were associated with a twofold increase in the risk of herpes zoster reactivation[33] and similar findings were reported in a prospective 8-year follow-up of 2568 adults.[34] A recent study found that among African-American women with asymptomatic HIV, those with PTSD caused by rape, physical assault and bereavement had a more rapid CD4 cell count decline.[35] A longitudinal study of homosexual men reported similar findings.[36] It is well known that women who have experienced rape more often experience depression, anxiety, PTSD, anger, shame, self-hate and self-blame.[37]

Rwandan women have increased risk for PTSD and depression due to the 1994 war and genocide in which approximately 250 000 women were raped, more than 65% of whom are infected with HIV, leading to further psychological trauma.[38 39] Our preliminary analysis in 936 HIV-infected and uninfected women recruited into the Rwanda Women's Interassociation Study and Assessment (RWISA), found a large difference in reported shingles in the last 6 months by HIV serostatus: 1% (n=2/226) versus 12.5% (n=89/710) in the HIV-uninfected and HIV-infected women, respectively.

We assessed the association between shingles and PTSD among HIV-infected Rwandan women who have a potentially increased risk of PTSD and depression.[40] A higher incidence of shingles in women with PTSD would provide evidence of clinical manifestation of PTSD-related immune suppression. This study can also provide clinicians with information that may help them to weigh the risks and benefits of providing the shingles vaccine to individual patients. This is the first study to our knowledge comparing the prevalence of herpes zoster reactivation (shingles) during the previous 6 months among CD4 cell count categories of HIV-infected Rwandan women and its association with PTSD, adjusting for depression, CD4 cell count and other potential confounders and mediators.

METHODS
Study population
This cross-sectional study was conducted as part of RWISA, an observational study designed to assess the impact of HIV and residual factors from the 1994 genocide in Rwandan women. The parent study was a prospective cohort study, and this was a cross-sectional analysis of the baseline data. It was approved by the Rwandan National Ethics Committee and the Institutional Review Board of Montefiore Medical Center (Bronx, New York, USA). All participants provided written informed consent and agreed to be tested or retested for HIV, and were able to successfully complete interviews in Kinyarwanda (the official language of Rwanda), travel to and from the research site, and participate in a baseline outpatient visit. In 2005, a total of 710 HIV-infected and 226 HIV-uninfected women enrolled with follow-up visits occurring every 6 months.

Participants were recruited through grassroots women's associations of people living with HIV infection and clinical care sites for HIV-infected patients. Eligible women had lived in Rwanda and were >15 years of age in 1994. Frequency matching during study enrolment resulted in 50% of both the enrolled HIV-positive and HIV-negative women reporting rape during the 1994 genocide.

All HIV-infected women had to be naive to antiretroviral therapy (ART) at enrolment with the allowed exception of single dose nevirapine to prevent mother-to-child HIV transmission. Trained interviewers collected demographic, medical, psychological and behavioural information necessary for assessing clinical status, disease progression, risks for exposure to HIV, PTSD and depression symptoms as well as the participants' experiences of trauma during the genocide. The trauma interview was performed at a separate visit occurring within 2 weeks after the enrolment visit. Participants who experienced emotional distress following the sensitive questions or recalling of events were counselled onsite and provided with debriefing and referral, if needed, for counselling by trauma counsellors with the study. Details about study participants' recruitment were previously described by Cohen et al[40] in their study which looked at improvement in post-traumatic stress disorder in post-conflict Rwandan women.

Case definition and secondary variables
Shingles history was ascertained through the question: 'Has your health care provider ever told you that you had

shingles?' Women responding 'yes' where then asked: 'How many episodes of shingles have you had in the past six months?" In addition to the questions, shingles-affected areas or post-recovery scars were assessed during physical examination. For this analysis, the outcome 'shingles' was defined as reporting one or more episodes of shingles within the past 6 months. At study enrolment, participants also answered questions about age, income, educational attainment, ability to read, and history of genocidal and non-genocidal physical or sexual abuse and trauma. Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CES-D), with the standard cut-off of 16 indicating clinically significant symptoms of depression and the cut-off of 27 indicating major depressive disorder.[41] PTSD was assessed with the Harvard Trauma Questionnaire (HTQ), a cross-culturally validated instrument measuring trauma and torture events and symptoms. A study psychologist trained the study's trauma counsellors (i) how to determine events experienced during the 1994 genocide, (ii) how to determine the patients' responses to these events, and (iii) how to use the HTQ.[42] Using methods previously described,[42] the HTQ was adapted to the Rwandan experience and the Kinyarwanda linguistic equivalent. The HTQ includes a measurement of PTSD, which assessed the three categories of symptoms required for a DSM-IV diagnosis: re-experiencing, avoidance and hyperarousal. Mean HTQ scores >2 meet DSM-IV diagnostic criteria for PTSD;[43] women with mean HTQ scores >2 were categorised as having PTSD in this study.

Height and weight were measured for lightly clothed subjects without shoes and body mass index (BMI) was calculated as weight (kg)/height (metres)^2. CD4 counts were determined with a FASCount (Becton and Dickinson, Immunocytometry Systems, San Jose, California, USA). HIV infection was diagnosed with an HIV-testing algorithm which used two commercial HIV-1 antibodies ELISA kits (Vironostika, bioMérieux, Boxtel, the Netherlands and Murex HIV-1.2, DiaSorin, Oxford, UK).

Statistical analysis

Data were analysed using STATA V.11.1 (StataCorp LP, College Station, Texas, USA). Descriptive statistical analyses including means, SDs, medians and IQRs were presented for continuous variables, and percentages for categorical variables by CD4 strata (>350, 200–350 and <200 cells/µL). Analysis of variance and t tests compared continuous variable distributions across CD4 strata and by reporting/non-reporting of shingles in the past 6 months, respectively. χ^2 Tests and logistic regression compared categorical variable distributions across CD4 strata and reporting versus not reporting shingles in the past 6 months. Forward stepwise selection logistic regression with a p value of 0.15 to enter and remain, built multivariate predictive models of shingles in the past 6 months. p Values less than 0.05 were considered statistically significant for all analysis.

RESULTS

Table 1 summarises the baseline demographic and clinical characteristics of the study participants by CD4 categories. Most baseline characteristics did not differ significantly among the three CD4 categories except reported shingles (p=0.02) and depressive symptoms (p<0.01). The overall prevalence of shingles was 12.5% (n=89/710). There was an inverse relationship between reported shingles prevalence and immunological status: prevalence was 7.6%, 12.3% and 16.7% in women with CD4 >350, 200–350 and <200 cells/µL, respectively (p=0.02).

Table 2 shows the results of bivariate analysis of the associations of demographic and clinical characteristics with shingles. In unadjusted analysis, women who experienced PTSD defined as HTQ ≥2 versus HTQ <2 (OR 1.6; 95% CI 1.01 to 2.66), mild to moderate depressive symptoms (CES-D 16–27) (OR 2.0; 95% CI 1.02 to 4.03) or major depressive symptoms (CES-D >27) (OR 2.4; 95% CI 1.19 to 5.98) were all significantly more likely to report shingles in the past 6 months. The odds that a woman with BMI >21 kg/m^2 had shingles in the past 6 months was 0.42 (95% CI 0.23 to 0.74) compared to women with BMI <18.5 kg/m^2. In addition, compared to women with higher immunological status (CD4 >500 cells/µL), women with severe HIV-induced immunological depression (CD4 <200 cells/µL) were significantly more likely to report shingles in the last 6 months (OR 2.4; 95% CI 1.31 to 4.55).

In the final multivariate stepwise model, PTSD (adjusted OR (aOR) 1.7; 95% CI 1.03 to 2.89) and CD4 <200 versus >350 cells/µL (aOR 2.4; 95% CI 1.23 to 4.81) were independently associated with reported shingles. In this adjusted model, age 30–40 years (aOR 0.52; 95% CI 0.30 to 0.93) versus age <30 years, and monthly earnings >US$64 (aOR 2.0; 95% CI 1.01 to 3.99) versus <US$18 were also independently associated with reported shingles. The adjusted odds of shingles did not differ for those older than 40 versus younger than 30 years.

Depressive symptoms showed a significant bivariate association with reported shingles. However, depressive symptoms did not show an independent association in final stepwise multivariate logistic regression. Neither BMI nor experience of genocidal or non-genocidal violence was independently associated with reported shingles in the past 6 months. In addition, when genocidal violence was forced into the stepwise model, it was not significantly associated with shingles and did not confound PTSD or CES-D (data not shown).

DISCUSSION

To our knowledge this is the first study assessing the association between shingles and PTSD among HIV-infected women. This analysis found that women with PTSD were almost twice as likely to report recent shingles (aOR 1.72; 95% CI 1.03 to 2.89). While depressive symptoms had a significant unadjusted association with shingles, this association was not seen in the adjusted models.

Table 1 Baseline demographic and clinical characteristics of HIV-infected RWISA participants (n=710)

Parameters	HIV-infected participants n=710			All subjects n=710	p Value*
	CD4 >350 n=197	CD4 200–350 n=268	CD4 <200 n=245		
Age, mean±SD, years	34.3±7.0	35.3±6.7.0	34.9±7.0	34.9±7.0	0.26
Monthly income, n (%)					
<10 000 Rwf (US$18)	66 (34.2)	98 (37.1)	87 (36.6)	251 (36.1)	0.41
10 000–35 000 Rwf	105 (54.4)	131 (49.6)	111 (46.6)	347 (49.9)	
>35 000 Rwf (US$64)	22 (11.4)	35 (13.3)	40 (16.8)	97 (14.0)	
Employment, n (%)	50 (25.4)	63 (23.5)	58 (23.7)	171 (24.1)	0.88
Schooling, n (%)					0.87
No schooling	48 (24.4)	59 (22.0)	57 (23.3)	164 (23.1)	
Some primary school	78 (39.6)	99 (36.9)	92 (37.6)	269 (37.9)	
Secondary or university	71 (36.0)	110 (41.0)	96 (39.2)	277 (39.0)	
Ability to read, n (%)	149 (75.6)	208 (77.6)	185 (75.5)	542 (76.3)	0.82
Electricity in house, n (%)	26 (13.2)	36 (13.4)	21 (8.6)	83 (11.7)	0.17
Non-genocidal rape, n (%)	24 (12.2)	38 (14.2)	40 (16.3)	102 (14.4)	0.46
Genocidal rape, n (%)	96 (48.7)	128 (47.7)	125 (51.0)	349 (49.2)	0.71
Body mass index, mean±SD (kg/m^2)	21.9±4.0	21.8±3.9	21.1±3.7	21.6±3.9	0.06
Body mass index category, n (%) (kg/m^2)					0.58
<18.5	38 (19.3)	46 (17.2)	50 (20.4)	134 (18.9)	
18.5–21	54 (27.4)	81 (30.2)	80 (32.7)	215 (30.3)	
>21	105 (53.3)	141 (52.6)	115 (46.9)	361 (50.9)	
CES-D, mean±SD	22.4±9.3	23.0±8.2	25.8±9.6	23.8±9.1	<0.001
CES-D category, n (%)					<0.01
CES-D <16	42. (22.0)	53 (20.7)	28 (12.2)	123 (18.2)	
CES-D 16–27	96 (50.3)	134 (52.3)	110 (48.0)	340 (50.3)	
CES-D >27	53 (27.8)	69 (27.0)	91 (39.7)	213 (31.5)	
HTQ, median (IQR)	2.1 (1.7–2.7)	2.1 (1.8–2.8)	2.2 (1.8–2.8)	2.1 (1.8–2.7)	0.60
PTSD, HTQ score category, n (%)					0.71
No, HTQ <2	84 (43.5)	108 (41.7)	95 (39.6)	287 (41.5)	
Yes, HTQ ≥2	109 (56.5)	151 (58.3)	145 (60.4)	405 (58.5)	
Shingles in the past 6 months, n (%)	15 (7.6)	33 (12.3)	41 (16.7)	89 (12.5)	0.02

*p<0.05.
p Value is for comparing all three HIV/CD4 groups. The χ^2 test was used for categorical variables and ANOVA for continuous variables.
CES-D, Center for Epidemiologic Studies Depression Scale; HTQ, Harvard Trauma Questionnaire Score; PTSD, post-traumatic stress disorder; Rwf, Rwandan francs (currency); RWISA, Rwanda Women's Interassociation Study and Assessment.

Several studies have explored the role of emotional stressors (acute and chronic) in both depression and PTSD through influence on HPA axis reactivity.[44 45] Interestingly, the direction of PTSD's effect on the HPA axis is different from that of depression. This may explain why PTSD remained independently associated with shingles in the final multivariate model of our study while depression did not.[46]

Several studies have found a direct or indirect association of shingles with HIV/immunological status.[8 16] As with these studies, we also found a strong independent association between lower CD4 cell count and a higher incidence of shingles in HIV-infected women. These findings are consistent with the results of the prospective study by Glaser et al[12] who reported that shingles incidence is associated with degree of immunosuppression in HIV-infected women, and that even women with high CD4 counts had a 10-fold greater risk of herpes zoster reactivation than HIV-uninfected women. Similar findings were obtained by Colebunders et al, McNulty et al, Melbye et al and Sivayathorn et al, among others.[11 13–15]

In contrast, a prospective population-based cohort study from Uganda[21] did not find a relationship between CD4 count and the incidence of herpes zoster. Engels et al[18] in their prospective study in two cohorts, HIV-infected haemophiliacs and HIV-infected homosexual men, found that shingles risk was relatively constant at CD4 cell counts >200 cells/mm^3 but increased steeply below this level.

We also found that higher monthly income was independently associated with reported shingles. Lower income represents lower socioeconomic status which influences many measures of health status. As compared to women below 30 years of age, being above 40 years of age was not found to be independently associated with reported shingles, whereas being 30–40 years old was significant for less shingles (aOR 0.5; 95% CI 0.29 to 0.93). This is surprising as older age is associated with a higher incidence of shingles in those not infected with HIV. However, Glaser et al[12] also did not find age to be an independent predictor of herpes zoster in HIV-infected women. HIV-infected women aged 30–40 years had a

Table 2 Association of demographic and clinical characteristics with shingles among RWISA participants

Covariates	Bivariate OR	Bivariate 95% CI	Multivariate OR	Multivariate 95% CI
Age, years				
<30	1.00		1.00	
30–40	0.69	0.40 to 1.17	0.52	0.29 to 0.93
>40	0.90	0.48 to 1.68	0.75	0.38 to 1.48
Monthly income, n (%)				
<10 000 Rwf (US$18)	1.00		1.00	
10 000–35 000 Rwf	0.79	0.48 to 1.29	0.96	0.55 to 1.67
>35 000 Rwf (US$64)	1.40	0.74 to 2.64	2.00*	1.00 to 3.99
Employment (yes vs no)	0.84	0.49 to 1.44		
Schooling				
No schooling	1.00			
Some primary school	0.80	0.45 to 1.42		
Secondary or university	0.89	0.50 to 1.56		
Ability to read (yes vs no)	0.87	0.53 to 1.46		
Electricity in house (yes vs no)	0.95	0.47 to 1.92		
Non-genocidal rape (yes vs no)	1.62	0.92 to 2.85	1.80	0.96 to 3.35
Genocidal rape (yes vs no)	1.45	0.93 to 2.28		
Body mass index (BMI) (kg/m^2)				
BMI <18.5	1.00		2.58	1.36 to 4.89
BMI 18.5–21	0.89	0.50 to 1.58	2.27	1.29 to 4.01
BMI >21	0.42**	0.23 to 0.74	1.00	
CD4 cell count, cells/µL				
HIV positive, CD4 >350	1.00			
HIV positive, CD4 200–350	1.70	0.90 to 3.23	1.92	0.96 to 3.85
HIV positive, CD4 <200	2.44**	1.31 to 4.55	2.43*	1.23 to 4.81
Depressive symptoms (CES-D ≥16)				
No (CES-D <16)	1.00			
Minor (CES-D 16–27)	2.00*	1.02 to 4.03		
Major (CES-D >27)	2.43*	1.19 to 5.98		
PTSD, HTQ ≥2 (yes vs no)	1.64*	1.01 to 2.66	1.72*	1.03 to 2.89

*p<0.05; **p<0.01.
CES-D, Center for Epidemiologic Studies Depression Scale; HTQ, Harvard Trauma Questionnaire; PTSD, post-traumatic stress disorder; Rwf, Rwandan francs (currency); RWISA, Rwanda Women's Interassociation Study and Assessment.

lower prevalence of PTSD (n=218, 56.33%) compared to women under 30 years of age (n=91, 59.48%) and over 40 years of age (n=96, 63.16%), which is not statistically significantly difference (p=0.33). In a multivariate stepwise model, age 30–40 versus <30 (aOR 0.5; 95% CI 1.02 to 0.93) remained significantly associated with shingles in the model after adjusting for PTSD.

This study has some limitations mainly due to the cross-sectional design (potential recall bias, causality, generalisability). The outcome 'shingles' was self-reported; however, the research interviewers were clinically trained (nursing) and had received training on how to differentiate between reported shingles and other conditions. In addition, the outcome was 'shingles in the past 6 months' which limited the potential for recall bias for events in the distant past. Another limitation of our analysis concerned the direction of the causality between shingles and PTSD. Perhaps prior occurrence of shingles could increase the risk for PTSD, although we believe that such is not likely due to the limited nature of shingles and patient knowledge that it would not re-occur.

In conclusion, our data demonstrated a statistically significant independent association of PTSD with reported recent shingles in HIV-infected women. This suggests that PTSD, a condition known to cause immune activation, may also be causing immune compromise resulting in shingles. This study also confirmed previous findings of a strong relationship between shingles and greater immunosuppression in women with HIV infection.

Further prospective studies to confirm our findings of PTSD and reported shingles are highly recommended.

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