PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	DEPRESSION AND RESILIENCE IN HIV-INFECTED WOMEN WITH EARLY LIFE STRESS: DOES TRAUMA PLAY A MEDIATING ROLE? A CROSS-SECTIONAL STUDY.
AUTHORS	Spies, Georgina; Seedat, Soraya

VERSION 1 - REVIEW

REVIEWER	Karl Goodkin AIDS Healthcare Foundation USA
REVIEW RETURNED	18-Nov-2013

GENERAL COMMENTS	There should not be any p values indicated as: ""00.00". It is more appropriate to express strength of relationship with beta weights than with p values This is a very well written MS of major interest to the field and to the readership of the Journal. The research question is addressed in an original manner, and the MS has many strengths. There is clear definition of the study objective as to whether trauma exposure and/or trauma symptomatology mediate the relationship between depressive symptomatology and resilience in HIV infected women with exposure to moderate-to-severe childhood trauma in South Africa. The study design is appropriate and well delineated. Ninety-five HIV infected women with early trauma event history were recruited from a study conducted at clinics in the Cape Town area in which neuropsychological testing and MRIs were required -- a convenience sample. In addition to obtaining background sociodemographics, CD4 cell count, and plasma viral load, participants were administered the CES-D for depressed mood level, the Life Events Checklist for traumatic life event exposure, the Childhood Trauma Questionnaire for childhood trauma exposure, the Davidson Trauma Scale for post-traumatic distress assessment, and the Connor-Davidson Resilience Scale to assess resiliency to stress. Statistics are used appropriately and explicitly to address the research question of mediation according to the classic Baron and Kenney model put forward in 1986. This analytic model has been under-utilized in the clinical literature to address research questions focused on mediation. The results here indicate that post-traumatic distress mediates the relationship between depressive symptoms and resilience whereas neither proximal nor distal measures of traumatic life event exposure do.

	It would be of interest to assess the impact of non-traumatic stressful life event exposure and related anxious mood, which might add to the capacity to predict the depression-resilience relationship. It would also be of interest to utilize a conceptual model of stress and coping. For example, as noted by the authors, social support and coping strategy are known to impact the relationship of stressful life event exposure to associated levels of distressed mood and might have added to the predictive utility of the traumatic life event exposure data obtained here. Of note related to this, it might be anticipated that two types of distress (trauma- and depression-related) would predict a third outcome (e.g., resilience) better then a single form of distress (i.e., depression-related distress) and a predictor of distress (e.g., traumatic stressful life events) since the life event predictor measure will have variance that is largely subsumed by the distress measure. It seems surprising that this sample should show an unusually high mean resilience score. This could be related to the study's entry criteria. For example, exclusion of recent use of psychotropics would exclude those with a history of more severe depressive symptoms and truncate the higher end of the depression-related distress range. The high plasma viral load of the sample suggests that control of clinical disease burden would be variable and of interest to examine regarding the relationship of interest between depression-related distress and resilience. This aspect could also be examined by comparing those treated and not treated with ART, for which there is an approximately equal split. Likewise, an examination of the impact of syndromal depression vs. depressed mood level would have been of interest. Exclusion of HCV infection would likely be yet more relevant than exclusion of HBV infection. It is not clear whether the authors have given consideration to what type of resilience-building intervention should be proposed on the basis of these results. While an intervention effective for both trauma- and depression-related distress is more directly supported, longitudinally interventions aimed at known predictors of distress might prove more effective. In conclusion, this study is well designed and analyzed resulting in the contribution of clinically significant, new knowledge to this important area of mediators of resilience in HIV-infected women as a population generally and in resource-limited countries such as South Africa in particular.

REVIEWER	Robert Stewart King's College London (Institute of Psychiatry), UK
REVIEW RETURNED	20-Dec-2013

GENERAL COMMENTS	1. The inclusion criterion of 'exposure to childhood trauma' is a little

	vague and it would be helpful for readers if the authors could describe a little more clearly the cut-off chosen (e.g. what counted as 'childhood trauma'?). 2. Do the authors have any information on numbers approached, numbers consenting and/or numbers excluded because of lack of trauma? And is there any information on characteristics of those included compared to those not included? Both elements would also help readers understand the nature of the analysed sample in relation to the source population. 3. The resilience scale is the main outcome but does not receive adequate levels of description. First, it should be named in the abstract. Second, there needs to be more information about the types of questions used. As the authors mention, the concept of 'resilience' remains a little heterogeneous in the literature so it is important to know what approach was taken here. In particular (very relevant to some of the findings), resilience might simply be regarded as the absence of mental disorder in people who have experienced a given level of trauma. Is the CD-RISC simply measuring the absence of mental disorder or other constructs as well? 4. Re p13, 'internal consistency' would be a better term for Cronbach alpha than 'reliability' 5. The authors mention that higher levels of resilience 'resulted in' lower depression/PTSD. This implies a direction of causation which cannot be inferred from a cross-sectional study and it would be preferable for 'associated with' to be used as a term instead. Although resilience is meant to be a stable construct, this has not been robustly demonstrated and it is entirely possible that people with depression under-rate their resilience. 6. Under the Sobel test heading in the Results, it's not completely clear what analyses the p-values are referring to. 7. For the final test of mediation it would be much more informative to look at the change (or not) in the IV-DV coefficient of interest following MV adjustment, rather than the change in the p-value.

VERSION 1 – AUTHOR RESPONSE

Please include the study design in the title.

This has been included.

The inclusion criterion of 'exposure to childhood trauma' is a little vague and it would be helpful for readers if the authors could describe a little more clearly the cut-off chosen (e.g. what counted as 'childhood trauma'?).

A score of 41 and higher on the CTQ was used as the cut-off. This information has been added. More detail about the scoring of the CTQ can also be found in the paragraph discussing the questionnaire.

Do the authors have any information on numbers approached, numbers consenting and/or numbers excluded because of lack of trauma? And is there any information on characteristics of those included compared to those not included? Both elements would also help readers understand the nature of the

analysed sample in relation to the source population.

As mentioned in the manuscript, 95 HIV-positive women with exposure to childhood trauma were selected from a larger prospective cognitive and imaging study. The larger sample/dataset (n = 230) consists of a mix of HIV-infected and uninfected women, with and without trauma exposure. So no participants were excluded because of a lack of trauma. They were just not the focus of the present study and form part of the larger study in which this study is embedded. Information has been added to the section of participants which will hopefully provide more clarity.

The resilience scale is the main outcome but does not receive adequate levels of description. First, it should be named in the abstract. Second, there needs to be more information about the types of questions used. As the authors mention, the concept of 'resilience' remains a little heterogeneous in the literature so it is important to know what approach was taken here. In particular (very relevant to some of the findings), resilience might simply be regarded as the absence of mental disorder in people who have experienced a given level of trauma. Is the CD-RISC simply measuring the absence of mental disorder or other constructs as well?

Thank-you for the suggestion. The CD-RISC has been named in the abstract as requested. More information regarding the types of questions has been added to the section describing the measure. The CD-RISC measures more than the absence of a mental disorder, it measures constructs such as hardiness, self-esteem/confidence, adaptability, problem solving, humor, faith etc.

Re p13, 'internal consistency' would be a better term for Cronbach alpha than 'reliability'

This has been changed.

The authors mention that higher levels of resilience 'resulted in' lower depression/PTSD. This implies a direction of causation which cannot be inferred from a cross-sectional study and it would be preferable for 'associated with' to be used as a term instead. Although resilience is meant to be a stable construct, this has not been robustly demonstrated and it is entirely possible that people with depression under-rate their resilience.

Thank-you for this suggestion. We agree that we cannot infer causality from a cross-sectional study design and we have changed this wording as suggested.

Under the Sobel test heading in the Results, it's not completely clear what analyses the p-values are referring to.

The p values are referring to the Sobel test for mediation. I have added the z value and its p value to make it clearer.

For the final test of mediation it would be much more informative to look at the change (or not) in the IV-DV coefficient of interest following MV adjustment, rather than the change in the p-value.

I have added the beta coefficients to this section so that one can look at the change in both the coefficient and in the p-value.

There should not be any p values indicated as: ""00.00". It is more appropriate to express strength of relationship with beta weights than with p values.

Beta values have been added as requested.

It would be of interest to assess the impact of non-traumatic stressful life event exposure and related anxious mood, which might add to the capacity to predict the depression-resilience relationship. It would also be of interest to utilize a conceptual model of stress and coping. For example, as noted by the authors, social support and coping strategy are known to impact the relationship of stressful life event exposure to associated levels of distressed mood and might have added to the predictive utility of the traumatic life event exposure data obtained here. Of note related to this, it might be anticipated that two types of distress (trauma- and depression-related) would predict a third outcome (e.g., resilience) better then a single form of distress (i.e., depression-related distress) and a predictor of distress (e.g., traumatic stressful life events) since the life event predictor measure will have variance that is largely subsumed by the distress measure.

Thank-you for these very useful and valid suggestions. I agree that it would be of interest to incorporate these suggestions, possibly in a future study? However, this will not be possible for this study as we do not have any data on non-traumatic stressful life event exposure. The Life Events Checklist includes stressful life events which are regarded as index traumas for the development of PTSD and this was the only measure used to capture data on stressful life events. We have added this to the manuscript as a limitation.

It seems surprising that this sample should show an unusually high mean resilience score. This could be related to the study's entry criteria. For example, exclusion of recent use of psychotropics would exclude those with a history of more severe depressive symptoms and truncate the higher end of the depression-related distress range. The high plasma viral load of the sample suggests that control of clinical disease burden would be variable and of interest to examine regarding the relationship of interest between depression-related distress and resilience. This aspect could also be examined by comparing those treated and not treated with ART, for which there is an approximately equal split. Likewise, an examination of the impact of syndromal depression vs. depressed mood level would have been of interest. Exclusion of HCV infection would likely be yet more relevant than exclusion of HBV infection. It is not clear whether the authors have given consideration to what type of resilience-building intervention should be proposed on the basis of these results. While an intervention effective for both trauma- and depression-related distress is more directly supported, longitudinally interventions aimed at known predictors of distress might prove more effective.

Agreed. Perhaps excluding individuals with recent or current use of psychotropic medication would exclude those with a history of more severe depressive symptoms. On the other hand, it must be noted that depression and anxiety are largely under diagnosed and under treated in routine HIV medical care, particularly in developing countries like South Africa. So it is not necessarily the case that the majority of individuals with more severe depressive symptoms would be on psychotropic medication.

The use of self-reported data for depression using the CES-D would not make an investigation of the impact of syndromal depression vs. depressed mood level possible but should be considered for future research in this area.

It would be of interest to compare those treated with ART and those not treated with ART but perhaps with larger numbers? Indeed there is an equal split but this would result in two groups consisting of 47 cases. One would have to question whether there would be enough power to examine this relationship.

Regarding the HBV infection. It must be noted that the inclusion and exclusion criteria presented are applicable to the larger imaging and cognitive study in which this study is embedded. However, no participants were excluded for HBV infection in the present study.

We are in agreement. Understanding how resilience can be enhanced is of great importance and perhaps while more challenging, it would indeed be more effective if interventions were aimed at targeting predictors of distress.