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**CONCEPT SHEET: REGIONAL ANALYSES**

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| **Steering Group approval date:** | *NA* |
| **Tracking number:** | *SA258* |
| **Title:** | Mental health, adherence to antiretroviral therapy, and viral suppression among adolescents and adults living with HIV in South Africa: a cohort study |
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| **Type of c0ncept** | *Select as appropriate:*  New concept – no linked conference abstract  New concept – linked to conference abstract which **has not been** approved by SG  New concept – linked to conference abstract which **has been** approved by SG  Existing concept – major revisions requiring SG approval |
| **Type of study** | *Select as appropriate:*  Full research study – multiple sites  Full research study – single site  Study protocol  Fast track study using existing dataset  Mathematical or methodological modelling *(indicate if this will use IeDEA-SA data)*  Systematic review |
| **Statisticians:**  **Email:** | Andreas Haas |
| **Data manager:**  **Email:** | Andreas Haas |
| **Where will statistical analyses be done?** | ISPM, University of Bern |
| **Required variables:** | Sociodemographic data, laboratory data, medication claims, outpatient claims, and hospital claims |
| **Target journal:** | JIAS |
| **Ethics:** | *Select as appropriate:*  This concept uses only the IeDEA-SA standard dataset and is covered by the core IeDEA-SA ethics approvals.  This concept requires additional collection of health-related data, measurements or tests, or sampling of biological material not included in the IeDEA-SA standard dataset. Additional ethics approval is required.\* (Describe ethical considerations for any additional data collection here, including responsible IRBs.) |
| **Milestones:** | *Circulation of concept sheet: <date>*  *Ethics approval (for additional data collection): <date>*  *Circulation of mature draft paper: <date>*  *Submission to target journal: <date>* |
| **Abstract:** (about 100 words) | **Background and objectives**  Mental health and substance use disorders (MSD) are highly prevalent among people living with HIV and associated with suboptimal HIV treatment outcomes. This study aims to investigate associations between mental illness, ART adherence, and viral suppression among South African adolescent and adults by sex and age.  **Methods**  Cohort study of HIV-positive adolescents and adults (aged 15 years or older) who are insured with a large South African Medicaid scheme and enrolled with the Aid for AIDS (AfA) programme. Mental health will be assessed based on ICD10 diagnoses from outpatient and hospital claims and adherence based on pharmacy claims. We will validate the adherence measure against virologic outcomes using receiver operating characteristic (ROC) regression, assess associations between mental health, adherence, and viral load suppression using mixed effects Poisson regression models with robust standard errors and a random intercept on participant level. We will perform a group-based longitudinal trajectory analysis to identify persons with similar adherence trajectories a k-means expectation-maximization algorithm. Finally, we will perform a multinomial logistic regression analysis to examine factors associated with adherence group affiliation. |
| **Outline:** (about 1000 words) | **Background**  South Africa has the largest HIV epidemic in the world. In 2019, 7.7 million people were living with HIV in South Africa, and over 5 million people were receiving antiretroviral therapy (ART).1 Widespread access to ART has dramatically improved the life expectancy of people living with HIV,2 but the long-term effectiveness of ART depends on lifelong retention in HIV care and adequate adherence to ART.3,4  Mental health and substance use disorders (MSD) are highly prevalent among people living with HIV.5–7 Studies have consistently identified higher rates of MSDs experienced by people living with HIV than those in the general population.8 In sub-Saharan Africa, the estimated prevalence of major depression in people living with HIV is 15.3%, and 27% of people living with HIV have depressive symptoms.9 The median prevalence of anxiety disorders in people living with HIV in developing countries is estimated at 22.8%.10 Prevalence rates of alcohol use disorder among people living with HIV in sub-Saharan Africa range from 7% to 31%.11  Mental health problems are associated with poor HIV treatment outcomes, including low adherence11–16, lack of viral load suppression17–20, poor retention in HIV care21 and increased mortality.20 The relationship between mental illness and suboptimal ART adherence has been studied extensively. In a meta-analysis of 27 studies from Sub-Saharan Africa, people living with HIV with depressive symptoms or major depression had 55% lower odds of achieving optimal ART adherence than people living with HIV without depressive symptoms.11 These results were confirmed by Uthman et al. in a meta-analysis of 111 studies conducted in low-, middle- and high-income countries.13 In a more recent meta-analysis of studies from Sub-Saharan Africa depression was a major determinant of non-adherence with an odds ratio 2.54 (95% CI 1.88 – 3.43)15. A systematic review by Azar et al. reported an association between alcohol use disorders and poor adherence to ART.16  In another meta-analysis, anxiety symptoms were associated with increased odds for suboptimal ART adherence (pooled odds ratio 1.59 95% CI 1.29 – 1.96). This association remained strong even after excluding those only recently started on ART (< 6month), with a pooled odds ratio of 1.61 (95% CI 1.18 – 2.20).12 To a lesser extent, PTSD was also associated with suboptimal adherence (pooled odds ratio 1.19 95% CI 1.03–1.37 ).14 The evidence was less clear for adolescents living with HIV. A meta-analysis of 15 studies from Sub-Saharan Africa could not demonstrate a definite association between psychiatric disorders and ART adherence.22  **Objectives and hypotheses**  This study aims to investigate associations between mental disorders, ART adherence, and viral suppression among beneficiaries of a large South African medial aid scheme by sex and age. We hypothesize that mental disorders are associated with suboptimal ART adherence and low viral suppression. Furthermore, we hypothesize that low adherence to ART mediates the relationship between mental disorders and viral suppression.  **Study design**  We will follow cohort of HIV-positive adolescents and adults who are insured with a large South African Medicaid scheme and enrolled with the Aid for AIDS (AfA) programme from their first documented ART use (baseline) to the end of insurance coverage, death, database closure, or completion of 5 years of follow-up, whichever occurs first.  **Eligibility criteria**  HIV-positive adolescents and adults aged 15 years or older, receiving ART for at least 6 months, who are insured with a large South African Medicaid scheme and enrolled with the AfA programme are eligible for this study. Individuals with missing sex or date of birth will be excluded.  **Key variables and definitions**  We will extract demographic, laboratory, medication claim, outpatient claim, and hospital claim data on beneficiaries registered with the Medicaid scheme from the IeDEA database. Pharmacy claims contain information on the active ingredients of drugs coded according to the Anatomical Therapeutic Chemical (ATC) classification system23, the drug strengths, the dispensed amount, and the date of dispensing. Outpatient and hospitalization claims contain International Classification of Diseases, 10th Revision (ICD-10)24 diagnoses.  Mental health: Mental health will be assessed based on ICD10 diagnoses from outpatient and hospital claims. We will categorize mental disorders into the following groups: organic mental disorders (ICD codes F00-09), substance use disorders (F10-F19), serious mental disorders such as schizophrenia spectrum disorders, psychotic, delusional, or bipolar disorders (F20-F29, and F31), depressive disorders (F32, F34.1, and F54) anxiety and related disorders (F40-F48), other mental disorders like a single manic episode, persistent mood affective disorders, eating disorders, sleep disorders, or unspecified mental disorders (F30, F34.0, F34.8, F34.9, F50-F53, and F55-99), and any mental disorder (F00-F99).  Adherence: We will assess adherence based on pharmacy claims for combination ARVs (J05AR), non-nucleoside reverse transcriptase inhibitors (J05AG), protease inhibitors (ATC code J05AE), integrase inhibitors (J05AJ), or entry inhibitors (J05AX) used in HIV treatment. We will calculate the duration of each claim by dividing the amount of active ingredient dispensed by the WHO defined daily average maintenance dose for adults (DDD).25 We assume that patients who refilled their prescriptions early, stockpiled unused drugs for later use. We will calculate patients’ continuous medication availability (CMA)26 in two steps. First, we assign the mean adherence value of an interval between two consecutive refills (or between the last refill and the end of the patient follow-up) to each day of the interval. The mean adherence will be calculated as the number of days covered by sufficient drug supply during the interval divided by the number of days of the interval. Second, we split patients’ follow-up time into consecutive 1, 2, 3, and 6-month intervals and averaged daily mean adherence values over each interval. The CMA definition (termed CMA9) has been developed by Allemann and colleagues who showed that it performed well in group-based adherence trajectory analysis.27 We will model CMA as continuous and as binary outcome. We will dichotomize CMA at a threshold of 80% and 90%.  Viral load suppression: We will define non-suppressed viral load (NVL) as an HIV RNA viral load greater or equal to 400 copies/mL. We will use thresholds of 200 copies/mL and 1000 copies/mL in sensitivity analyses.  **Statistical methods**  We will describe characteristics of participants by mental health status at the end of follow-up using summary statistics. To validate the adherence measure (CMA), we will estimate the true-positive rate (sensitivity), false-positive rate (1-specificity), and area under the curve (AUC) of CMA measured in 1, 3, and 6 months before viral load testing for predicting NVL at a threshold of ≥400 copies/mL using receiver operating characteristic (ROC) logistic regression models with probit link by maximum likelihood estimation. Standard errors will be adjusted for clustering of observations within patients.  We will estimated unadjusted and adjusted risk ratios for differences in optimal vs. suboptimal 6-monthly CMA between persons with and without mental health diagnoses, between men and women, and between age groups using mixed effects Poisson regression models with robust standard errors and a random intercept on participant level.28 Each unadjusted model includes a binary variable for the mental health diagnosis, a categorical variable for time (half-year since baseline), and an interaction term for the mental health diagnosis and time. We will fit two adjusted models. Model 1 includes binary variables for any mental disorder and sex, categorical variables for age group and time, interaction terms for any mental disorder and time, sex, and age group, and an interaction term for age group and sex. Model 2 includes binary variables for each of the five groups of mental disorders and sex, categorical variables for age group and time, interaction terms for each of the five groups of mental disorders and time, and an interaction term for age group and sex. Mean differences will be estimated using contrasts. We will fit a linear regression model We will estimate and plot the 6-monthly mean CMA during the 1st and 5th half-year after baseline for people with and without mental health diagnoses by age group and sex using a linear regression model with robust standard errors and predictive margins.  We will estimate unadjusted and adjusted risk ratios for associations between mental health status and non-suppressed viral load (viral load ≥400 copies/mL) using mixed effects Poisson regression models with robust standard errors and a random intercept on participant level.28 Unadjusted model include a binary variables for mental health diagnosis, a categorical variable for time (year since baseline), and an interaction term for mental health diagnosis and time. We will fit four adjusted models. Model 1 includes binary variables for any mental disorder and sex, categorical variables for age group and time, interaction terms for any mental disorder and time, sex, and age group, and an interaction term for age group and sex. Model 2 includes model 1 variables and a categorical variable for CMA. Model 3 includes binary variables for each of the five groups of mental disorders and sex, categorical variables for age group and time, interaction terms for each of the five groups of mental disorders and time, and an interaction term for age group and sex. Model 4 includes model 3 variables and a categorical variable for CMA. Differences in the risk of NVL will be estimated using contrasts. We estimated and plotted the probability of viral suppression (viral load < 400 copies) at 2 years after baseline for people with and without mental health diagnoses by age group and sex based on model 1 using predictive margins.  We will perform a group-based longitudinal trajectory analysis to identify persons with similar adherence trajectories using the R package kml.29 The package implements a k-means expectation-maximization algorithm to cluster observations with homogeneous longitudinal trajectories into distinct groups. For the trajectory analysis, we will calculate participants’ 3-monthly CMA scores over five years from baseline. Persons with less than 3 years of follow-up will be excluded. We will impute missing CMA values for participants with less than 5 years of follow-up based on participants’ trajectory means. We will run the algorithm five times to identify two to six distinct groups and choose the optimal group size based on clinical relevance and the quality criteria of Calinski Harabatz and Ray Turi.29  We will estimate and plot the mean CMA and 95% CIs for each adherence group using Kernel-weighted local polynomial smoothing. Finally, we will perform a multinomial logistic regression analysis to examine factors associated with adherence group affiliation. The regression model includes a categorical variables for age group, binary variables for sex and mental health diagnosis at baseline, and an interaction term for age group and sex. Using predictive margins, we estimated and plotted the probability of group affiliation by sex, age, and mental health status.  Statistical analysis will be done in Stata (Version 16) and R (R version 3.6.3).  **References**  1 Joint United Nations Programme on HIV/AIDS (UNAIDS). AIDSInfo online database. https://aidsinfo.unaids.org/ (accessed Aug 26, 2020).  2 Johnson LF, Mossong J, Dorrington RE, *et al.* Life expectancies of South African adults starting antiretroviral treatment: collaborative analysis of cohort studies. *PLoS Med* 2013; **10**: e1001418.  3 Haas AD, Zaniewski E, Anderegg N, *et al.* Retention and mortality on antiretroviral therapy in sub-Saharan Africa: collaborative analyses of HIV treatment programmes. *J Int AIDS Soc* 2018; **21**: e25084.  4 Ford N, Darder M, Spelman T, Maclean E, Mills E, Boulle A. 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