

Recognizing and Understanding Risk of Depression in HIV Pre- Exposure Prophylaxis Studies

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Purpose

- To address the prevalence of depression in African countries, facts about depression and tenofovir, and information from other studies using tenofovir.

Outline

- Case
- Background on depression
- Depression in sub-Saharan Africa
- Determinants of suicidal behavior
- Experience with tenofovir and tenofovir containing antiretrovirals
- Discussion/Questions

Case

- 23 yo South African VOICE study participant (on oral product) is found at home shortly after ingesting house-cleaning fluid. She is emergently transported to the local hospital, where she is admitted in critical condition. She is treated supportively and physically recovers well. Her hospital team request the consultation of a psychiatrist.

BACKGROUND ON DEPRESSION

Depression

- Depression is ranked as the leading cause of disability worldwide and affects around 120 million people.

Depression

- Rates of major depressive disorder (MDD) vary widely in parts of Africa and are up to two times those seen in the West, despite similar assessment tools
- Reasons for this
 - Harsh social/economic conditions
 - Civil discord
 - HIV/AIDS

Broadhead JC, Abas M, *Psychol Med* 1998

Orley JH, Wing JK, *Arch Gen Psychiatry* 1979

HEALTH AND DEPRESSION IN SUB-SAHARAN AFRICA

Health in Sub-Saharan Africa

- The Global Burden of Disease (GBD) study determined that the highest disease burden in 1990 (21.4% of the global total) was in sub-Saharan Africa

Murray and Lopez, *Lancet*. 1997

Suliman et al. *Jnl of Nervous and Mental Dis*. 2010

Depression in Sub-Saharan Africa

- In 2002, depression accounted for 4.5% of the worldwide total burden of disease (in terms of disability-adjusted life years).
- Only one quarter of South Africans experiencing psychiatric illness receive treatment

World Health Organization, 2001

Seedat et al. *Social Psychiatry and Psychiatric Epidemiology* 2008

Screening Tools/Instruments to Evaluate Depression

- WHO Composite International Diagnostic Interview (CIDI): used in the South Africa Stress and Health Study (SASH)
- Face to face interviews (e.g. Mini – International Neuropsychiatry Interview)
- Self-reporting questionnaires (SRQ)
- Hopkins Symptom Checklist

Kaaya SF, et al. *Acta Psychiatr Scand* 2002.

Tomlinson et al. *S Afr Med J*. 2009

IMPACT OF HIV/AIDS ON DEPRESSION

HIV/AIDS and Depression

- Studies clearly document increased incidence of psychiatric disorders among people living with HIV/AIDS
- Depression, while associated with HIV infection has also been shown to be associated with those at high risk of HIV acquisition

HIV/AIDS and Depression

- Factors associated with depression include low income, poor access to medical care
- *Perception of discrimination in access to health care and reduced access to household financial resources following an HIV diagnosis were significantly associated with depression*

COUNTRY BREAKDOWN

SOUTH AFRICA

Mental Health in South Africa

- A national household survey was conducted between 2002 and 2004 using interviews to establish a diagnosis of depression.
- The dataset analysed included 4,351 adult South Africans of all racial groups.

Mental Health in South Africa

- **RESULTS:** The prevalence of major depression was 9.7% for lifetime and 4.9% for the 12 months prior to the interview. The prevalence of depression was significantly higher among females than among males.

Mental Health in South Africa

- The prevalence was also higher among those with a low level of education. Over 90% of all respondents with depression reported global role impairment.

Mental Health in South Africa

- Another study in South Africa highlighted the following “missed opportunities” among individuals presenting for primary care:
 - Depression/anxiety (28%)
 - Substance use (8%)
 - Suicide (7%)
- Individuals with depression/anxiety and substance abuse had high rates of somatic complaints

UGANDA

Mental Health in Uganda

- Prevalence of probable major depressive disorder (per Hopkins symptom checklist) in rural Uganda: 29.3%
- Relevant factors
 - Gender
 - Ecological factors
 - Indices of poverty and deprivation
 - Education
 - Employment
 - Family dynamics

Mental Health in Uganda

- Associations among women
 - Female gender independently associated with probable major depressive disorder (34.7% among females compared with 24.2% among males (OR 1.7; 95% CI 1.5-1.9)
 - Separated/widowed (OR of 3.0; 95% CI 2.4-3.9)
 - No formal education (OR of 1.4; 95% CI 1.1-1.8)

ZIMBABWE

Mental Health in Zimbabwe

- 1980s: WHO self reporting questionnaire was used to evaluate symptoms of depression
- 1990s: Shona symptom questionnaire (SSQ), written in the local language, was developed
- Validity of SSQ with WHO self-reported questionnaire demonstrated

Hall, A et al. *Cent Afr J Med* 1987

Patel V et al. *Acta Psych Scand* 1997

Patel V et al. *Int J Meth Psych Res* 1996

Mental Health in Zimbabwe

- One-quarter of people attending primary care and one-third attending traditional healers met criteria for depression
- Community surveys targeting lower income urban settings in Zimbabwe found prevalence of upwards of 50% among women

Patel V, et al. *BMJ* 2001

Broadhead J, Abas M. *Psychol Med* 1998

Mental Health in Zimbabwe

- Life events associated with depression at 12 months
 - Marital/relationship turmoil
 - Family/community deaths
 - Events directly related to infertility
 - Unwanted pregnancy

MALAWI

Mental Health Malawi

- Mental health research in Malawi is limited
 - Cross sectional study in rural Malawi evaluating depression and anxiety among mothers of young infants (n of 501 young women)
 - Study utilized Self-Reporting Questionnaire in Chichewa

Mental Health Malawi

- Prevalence of current depressive episode: 13.9% (95% CI 8.2-19.5%)
 - Low socioeconomic status
 - Inadequate relationships in life
 - Recent infant illness
 - Amongst those who knew their status, HIV infection

Case, continued...

- 23 yo South African VOICE study participant (on oral product) is found at home shortly after ingesting house-cleaning fluid. She is emergently transported to the local hospital, where she is admitted in critical condition. She is treated supportively and physically recovers well. Her hospital team requests the consultation of a psychiatrist.
- The psychiatrist unravels various stressors: history of childhood abuse, domestic disputes with husband and frequent arguments over money.

DETERMINANTS OF SUICIDAL BEHAVIOR

Suicidal Ideation

- Almost one million people commit suicide every year, 86% of them live in low- and middle-income countries.
- Suicidal ideation (parasuicidal behavior) occurs among women globally but is quite heterogenous in its cultural context

Suicidal Ideation

- Globally, girls and women have higher rates of suicidal ideation and behavior but lower rates of suicide mortality than boys and men
- 31-57% of suicide attempts are NOT associated with prior psychiatric disorder according to recent mental health surveys

Suicidal ideation

- Cross-national analysis of 21 countries with >100,000 respondents over age 18 via structured interviews (WHO World Mental Health Surveys)
- Lifetime suicide ideation and attempts reported by 9.6% and 2.8% respectively in the pooled sample

Suicidal Ideation

- Associated traumatic events
 - Death of a loved one (30.5%)
 - Witnessing violence (21.8%)
 - Interpersonal violence (18.8%)
 - Exposure to war (16.2%)

**EXPERIENCE WITH TENOFOVIR AND
TENOFOVIR CONTAINING
ANTIRETROVIRALS**

Tenofovir Disoproxil Fumarate (Tenofovir DF, TDF, VIREAD®)

Per **DAIDS** Regulatory Support Center

- Upset stomach, vomiting, gas, loose or watery stools
- Generalized weakness
- Dizziness
- Depression
- Headache
- Abdominal pain
- Worsening or new kidney damage or failure
- Inflammation or swelling and possible damage to the pancreas and liver
- Shortness of breath
- Rash
- Bone pain and bone changes such as thinning and softening which may increase the risk of breakage
- Muscle pain and muscle weakness

Emtricitabine (FTC, Emtriva™)

Per **DAIDS** Regulatory Support Center

- Headache
- Dizziness
- Tiredness
- Inability to sleep, unusual dreams
- Loose or watery stools
- Upset stomach (nausea) or vomiting
- Abdominal pain
- Rash, itching, which sometimes can be a sign of an allergic reaction
- Skin darkening of the palms and/or soles
- Increased cough
- Runny nose
- Abnormal liver function tests, which could mean liver damage
- Increases in pancreatic enzyme (substances in the blood), which could mean a problem with the pancreas
- Increased triglycerides
- Increased creatine phosphokinase (CPK), which could mean muscle damage

Tenofovir

- Gilead Sciences package insert for Viread®
 - Depression not mentioned in “Warning and Precautions” or “Adverse Reactions” sections
 - Study 903 comparing TDF/3TC/EFV with d4T/3TC/EFV
 - Depression (Grade 2-4) occurred in 11% in tenofovir containing arms versus 10% in arm without tenofovir

Tenofovir

- Safety profiles in tenofovir-containing trials (902, 907)
 - Most common AEs (occurring in similar rates to placebo):
 - GI (nausea/vomiting/diarrhea)

Observed Suicides and Suicide Attempts in PrEP Studies Worldwide

STUDY	COUNTRIES	STUDY POPULATION	INTERVENTION ARMS	INCIDENTS*
iPrEx	Brazil, Ecuador, Peru, South Africa, Thailand, USA	>2,500 MSM	Daily oral TDF/FTC (Truvada™)	9 attempts
HPTN 052	Botswana, Malawi	1,763 HIV serodiscordant couples	ART upon enrollment or ART within or below CD4 200-250	13 attempts (3 completed suicides)
MTN 003 (VOICE)	South Africa, Uganda, Zimbabwe	1,494 heterosexual women	TDF 1% topical gel; oral TDF; oral TDF/FTC	3

*Depression requiring hospitalization, suicidal ideation/attempt, completed suicide

Case, continued

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- The psychiatrist unravels various stressors: history of childhood abuse, domestic disputes with husband and frequent arguments over money.

Case

- The psychiatrist recommends ongoing weekly one on one counseling sessions
- The patient is discharged from the hospital in the care of her husband
- She returns to clinic at her next scheduled visit and reports that she would like to stay in the study

Discussion

- How should we be screening for depression?
- If depression is noted, is there a role for pharmacotherapy for study participants?
- When should we refer to psychiatric care/mental health professionals?
- What is our responsibility to our participants?
- How are we, in some cases, the safety net for women who are at risk for suicide?

Discussion

- How do we explore the role of men in the context of social harms and influences on women's choice to participate in HIV prevention studies?

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