# THE PSYCHOSOCIAL AND MEDICAL INTERSECTION OF HIV AND EPILEPSY IN ZAMBIA

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## ABSTRACT

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Human Immunodeficiency Virus (HIV) has transformed from a deadly disease to a chronic condition. As a result, the number of conditions occurring with HIV is increasing dramatically. In sub-Saharan Africa, epilepsy is the most common chronic neurological disorder. The probability that someone will have both HIV and epilepsy is substantial. In addition, new-onset seizure occurs in more than 10% of HIV-positive adults and people with epilepsy are more vulnerable to HIV infection than people without epilepsy. Little is known about the psychosocial and medical burden faced by people with both conditions.

HIV and epilepsy are associated with disease-associated stigma, however, it is unclear whether comorbid HIV and epilepsy is associated with increased reported stigma ("layered stigma"). To assess layered stigma, we first examined the measurement properties of the 24-item Stigma Scale of Epilepsy (SSE) to determine whether it more adequately captures stigma from the perspective of individuals with epilepsy than the commonly used 3-item Stigma Scale. We found that the SSE assessed two underlying traits, whereas the 3-item Stigma Scale only assesses one, suggesting that the SSE may be a more complete measure of felt stigma. We then used the SSE, the HIV/AIDS Stigma Instrument – PLWA, and Jacoby's 3-item Stigma Scale to assess HIV-related stigma and epilepsy-associated stigma reported by people with HIV & epilepsy, people with epilepsy only, and people with HIV only. Comorbid HIV infection and epilepsy was

associated with moderately increased HIV-related stigma. No significant differences in epilepsy-associated stigma were found.

We then examined medication side effects to determine whether cotreatment with antiretroviral drugs (cART) for HIV and an enzyme-inducing antiepileptic drug (EI-AED) for epilepsy was associated with increased adverse events. As there is limited data regarding side effects from antiepileptic drugs prescribed routinely in resource-limited settings, we first assessed adverse events experienced by Zambian people with epilepsy taking a stable dose of phenobarbital. Participants reported a mean of five side effects, which suggests that phenobarbital is may not be as well tolerated as previous studies suggest. We then assessed adverse events reported by HIV-positive individuals initiating cART with an EI-AED and compared them to adverse events reported by individuals initiating cART only and individuals with untreated HIV infection. Adverse events were assessed again two weeks later for individuals initiating cART with an EI-AED and cART only. We found that, despite having a higher CD4+ T-cell count, individuals initiating cART and an EI-AED were generally more symptomatic at baseline than individuals in the other treatment groups. In addition, more participants in the cART+EI-AED group reported experiencing nausea or vomiting at follow up than at baseline using paired t-tests.

This dissertation quantified some of the medical and psychosocial challenges faced by people with HIV and epilepsy. Understanding these challenges is essential to providing optimal care to patients with comorbid HIV and epilepsy. Additional research examining layered stigma and medication adverse effects among people with comorbid HIV and epilepsy is warranted.

To the patients and staff at the University Teaching Hospital in Lusaka, Zambia.

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## KEY TO ABBREVIATIONS

| | |
|---|---|
| [X] | Plasma Concentration of X |
| ↑ | Increase |
| ↓ | Decrease |
| ↔ | No effect |
| 3TC | Lamivudine |
| ABC | Abacavir |
| AE | Adverse Event |
| AED | Antiepileptic Drug |
| AIDC | Adult Infectious Disease Centre |
| AIDS | Acquired Immunodeficiency Syndrome |
| ALT | Alanine Transferase |
| ARV | Antiretroviral Drug |
| ATT | Anti-Tuberculosis Treatment |
| ATV/r | Atazanavir/ritonavir |
| AZT | Zidovudine |
| BD | Twice Daily *(bis in die)* |
| cART | Combination antiretroviral therapy |
| cART+EI-AED | Combination Antiretroviral and Enzyme-Inducing Antiepileptic Drug |
| CBZ | Carbamazepine |
| CHASE | Cohort Study of HIV-Associated Seizures and Epilepsy |
| CI | 95% Confidence Interval |

| | |
|---|---|
| CNS | Central Nervous System |
| CYP | Cytochrome P450 Enzyme System |
| CYP450 | Cytochrome P450 Enzyme |
| D4T | Stavudine |
| DALY | Disability Adjusted Life Year |
| ddI | Didanosine |
| ECT | Epilepsy Care Team |
| EFV | Efavirenz |
| EI-AED | Enzyme-Inducing AED |
| FDA | Food and Drug Administration |
| FTC | Emtricitabine |
| HASI-P | HIV/AIDS Stigma Instrument-PLWA |
| HIV | Human Immunodeficiency Virus |
| IBE | International Bureau for Epilepsy |
| ILAE | International League Against Epilepsy |
| IRT | Item Response Theory modeling |
| KAP | Knowledge, Attitudes, and Practices |
| LEAP | Liverpool Adverse Events Profile |
| LPV/r | Lopinavir/ritonavir |
| LT | Likert-type Responses |
| MSU BIRB | Michigan State University Biomedical Institutional Review Board |
| N | Number |
| NIH | National Institutes of Health |

| | |
|---|---|
| NNRTI | Non-Nucleoside Reverse Transcriptase Inhibitor |
| NRTI | Nucleoside Reverse Transcriptase Inhibitor |
| NVP | Nevirapine |
| OD | Once Daily *(omne in die)* |
| OR | Odds Ratio |
| PB | Phenobarbital/Phenobarbitone |
| PHT | Phenytoin |
| PI | Protease Inhibitor |
| PLWA | People Living with HIV/AIDS |
| PRM | Primidone |
| PWE | People with Epilepsy |
| SARS | Severe Acute Respiratory Syndrome |
| SD | *If used prior to a drug name or abbreviation*: Single Dose |
| | *If used in parenthesis after the word "mean":* Standard Deviation |
| SE | Standard Error |
| SSE | Stigma Scale of Epilepsy |
| SSQ | Shona Symptom Questionnaire |
| $t_{½}$ | Half-life |
| TB | Tuberculosis |
| TDF | Tenofovir |
| TMP/SMX | Trimethoprim/Sulfamethoxazole |
| UGT | UDP-glucuronosyltransferase System |
| UNZA BREC | University of Zambia Biomedical Research Ethics Board |

| | |
|---|---|
| USD | United States Dollars |
| UTH | University Teaching Hospital |
| VA | Valproic Acid/Valproate |
| WHO | World Health Organization |
| YLDs | Years Lived with Disability |
| zMMSE | Zambian Mini-Mental Status Exam |

# CHAPTER ONE:

# BACKGROUND AND OBJECTIVES

## BACKGROUND

### Human Immunodeficiency Virus

Human Immunodeficiency Virus (HIV) infection and Acquired Immunodeficiency Syndrome (AIDS) remain the fifth greatest cause of global disease burden, despite substantial international effort to provide treatment and reduce transmission [1]. In 2012, an estimated 35.3 million people were living with HIV/AIDS worldwide [2,3]. Although primary prevention efforts have led to a decrease in the incidence of HIV infection, a simultaneous decline in AIDS-related deaths has resulted in an increase in overall HIV prevalence [4,5,2]. Expanded access to antiretroviral drugs (ARVs), especially in sub-Saharan Africa, is primarily responsible for this reduction in mortality [6,7]. As the availability of ARVs continues to improve, it is anticipated that the number of people living with AIDS (PLWA) will continue to increase [7].

The burden of HIV affects a heterogeneous group of individuals who are unevenly distributed across the globe [1,8]. Sub-Saharan Africa accounts for 70.9% of the 4,342,000 global Disability Adjusted Life Years (DALYs) associated with HIV [1]. In this region, unprotected heterosexual intercourse is the most frequent mode of HIV transmission and, as a result, young adults, especially young women, are more likely to be HIV-positive [7]. Mother-to-child transmission of HIV continues to account for a substantial number of new HIV infections among children [9,10]. Although countries around the world have adopted multifaceted HIV prevention strategies to decrease heterosexual and mother-to-child transmission of HIV [3], these programs have had mixed success in sub-Saharan Africa [2]. This

suggests that, in this setting, HIV will continue to affect individuals of all ages for the foreseeable future. As HIV-positive individuals continue to live longer, the number of comorbidities will continue to grow in this diverse population [11,12]. To control HIV both at the level of the individual and the population, these comorbid conditions must be recognized and appropriately managed [12].

**Epilepsy**

Epilepsy affects an estimated 70 million people worldwide [13,14], and seizure disorders are particularly common in HIV-infected persons, with a reported prevalence of approximately 11% [15-17]. Characterized by sudden, recurrent seizures, epilepsy disproportionately affects individuals residing in developing countries [13,14]. Eighty-five percent of people with epilepsy reside in low and lower-middle income countries where preventable causes of epilepsy, such as trauma, pre- and perinatal injury, and central nervous system (CNS) infections, are more prevalent than in high-income countries [18,13,19]. Unlike high-income countries, where the age of onset of epilepsy is bimodal and is highest among children and the elderly, epilepsy incidence in low- and low-middle income countries appears to be greatest in young adults [18]. Research conducted in low- and low-middle income countries suggests that epilepsy in this setting is likely associated with substantial mortality, especially in rural areas [14,20-23,18].

Antiepileptic drugs (AEDs) can reduce seizure recurrence in approximately 70% of people with epilepsy [24,25]. However, a considerable international AED treatment gap exists. There is a substantial disparity between the number of individuals with active epilepsy and the number of individuals whose seizures are being appropriately treated with AEDs [26,27,18,28,25]. Although the epilepsy treatment gap exceeds 50% in low-middle income

countries, the gap is 75% or greater in most low-income countries [27]. To ameliorate this inequality, International Bureau for Epilepsy (IBE), International League Against Epilepsy (ILAE), and World Health Organization (WHO) have joined forces for the Global Campaign Against Epilepsy [13,29,30]. A mathematical analysis suggests that 1,360 annual DALYs per one million people could be saved by making older antiepileptic drugs accessible in 50% of sub-Saharan African primary healthcare facilities [31]. Improved management of epilepsy by increasing the availability of AEDs for people with epilepsy in low- and low-middle income settings like sub-Saharan Africa would result in reduced morbidity and mortality [32,33].

**HIV & Epilepsy**

There is the potential for substantial overlap between HIV and epilepsy, especially in sub-Saharan Africa. In eastern sub-Saharan Africa,[a] HIV and epilepsy are ranked 11$^{th}$ and 13$^{th}$, respectively, in terms of accounting for the greatest number of years lived with disability (YLDs) [5]. As HIV infection and epilepsy are not mutually exclusive, the likelihood that an individual could develop HIV and epilepsy independently of one another in eastern sub-Saharan Africa is substantial. HIV itself may lead to the development of epilepsy. HIV can directly invade the brain and, by eliminating immune cells, predispose individuals to CNS opportunistic infections [34] that can present as seizures [35-37]. Hospital-based cohort studies have suggested that new-onset convulsions are common in HIV-infected persons, and seizure is a presenting symptom in 2-13% of HIV-positive adults [38-40,15,41,16]. Unfortunately, these studies may have

[a] Global Burden of Disease 2010 region consists of Burundi, Comoros, Djibouti, Eritrea, Ethiopia, Kenya, Madagascar, Malawi, Mauritius, Mozambique, Rwanda, Seychelles, Somalia, Sudan, United Republic of Tanzania, Uganda, and Zambia.

underestimated the incidence of seizure in HIV-infected adults, as they were often retrospective and reliant on documentation of seizure occurrence in patient charts [15,41,40,16]. In addition, it is unclear what proportion of HIV-positive patients presenting with new-onset seizures eventually go on to develop epilepsy and require treatment with AEDs. Estimates for the development of epilepsy after new-onset seizure vary widely for the general population [42].

HIV-positive individuals with comorbid epilepsy may face considerable social and medical challenges, such as disease-associated stigma and drug interactions, that could complicate the management of both conditions. Understanding the challenges associated with HIV and epilepsy, and how they intersect, is essential to providing optimal care to these patients.

**Disease-Associated Stigma**

Stigma remains a substantial problem for people with either HIV or epilepsy. During the time of the ancient Greeks, the word "stigma" referred to a physical brand that marked slaves and criminals so that they could be easily differentiated from full citizens [43-45]. Over time, the concept of stigma has evolved to include numerous visible and concealable attributes that are deviations from an individual's expected social identity [44]. Like criminality, these attributes are viewed negatively by society and, as a result, the general public often labels, stereotypes, and discriminates against individuals with the trait [46,47].

There are multiple theoretical perspectives on stigma [46,48-51] and, as a result, there is often confusion regarding terminology. When examining the process of stigmatization, people

are divided into individuals who are affected by the condition and individuals who are not[b].

Unaffected individuals believe that individuals who are affected by conditions such as HIV or epilepsy possess a threatening stigma that may have been acquired via socially unacceptable behavior and, as a result, distance themselves from those affected by the condition. This is done via negative emotional responses to the condition (prejudice); applying society's popular beliefs to the affected (stereotyping); and acting on prejudices and stereotypes to the detriment of the affected (discrimination) [52,50]. Discrimination directed at a stigmatized individual by the general public is commonly referred to as *enacted stigma* [53-55]. Enacted stigma can originate either from individuals or society. *Interpersonal stigma* describes enacted stigma originating from the actions of an unaffected individual [54,56], whereas *institutionalized stigma* describes the status loss and discrimination that result due to society's laws and traditions [57]. When examining stigmatized conditions, institutionalized stigma is often neglected, to the extent that enacted stigma is frequently used as a synonym for interpersonal stigma.

Affected individuals are reminded that their condition is socially unacceptable by: their awareness of stigma regarding their condition in their community; their belief that they will be stigmatized against by others in the future; and their own self-stigmatization. An individual's awareness of stigma in his community (*felt normative stigma*) is influenced by his own past experiences with enacted stigma as well as by stories of discrimination against others with the same condition (*vicarious stigma*) [56]. An affected individual's belief that he will encounter interpersonal stigma in the future is referred to as *anticipated stigma* and is often associated with

[b] For some conditions, there is likely a third group those whose status is unclear (i.e. HIV-positive, negative, and unknown status). Although this may affect disease prevention efforts, it will not be addressed here.

fear [58,50]. Lastly, the self-stigmatization that occurs in affected individuals is *internalized stigma* and is often associated with a negative self-image [57,58]. *Felt stigma* is a term commonly employed when examining stigma associated with epilepsy and encompasses both anticipated and internalized stigma [54,53]; it is not synonymous with felt normative stigma. Research suggests that individuals may moderate the extent to which they feel stigmatized by adjusting their response to and interpretation of popularly held-beliefs regarding their condition [59,60]. The term "perceived stigma" has been used both used as a synonym for felt stigma [61], experiences with enacted stigma [58], as well as a non-specific term to describe stigma from the perspective of an affected individual [62,63].

Figure 1.1 illustrates the relationships between the different mechanisms of disease-associated stigma. Individuals affected by HIV and epilepsy often respond to stigma by developing strategies to avoid disclosure of their condition [50,44,53,52,64,65,57]. All mechanisms of disease-associated stigma are mediated by the extent to which the individuals involved (both affected and unaffected) subscribe to social norms regarding HIV and epilepsy [66,60,67].

Considerable research has sought to examine the social process of stigmatization because of its impact on the opportunities and well-being of the affected individual [68,46]. Stigmatization varies both with the characteristics of the stigmatized condition and individual affected [52]. Illness-related characteristics that are associated with stigmatization are concealment and responsibility [69]. Concealment refers to the extent that an individual is able to hide his illness from others [70,58], whereas responsibility refers to the degree to which society believes the affected individual should be held accountable for developing his condition. These illness-related characteristics are closely tied to cultural beliefs and may vary widely

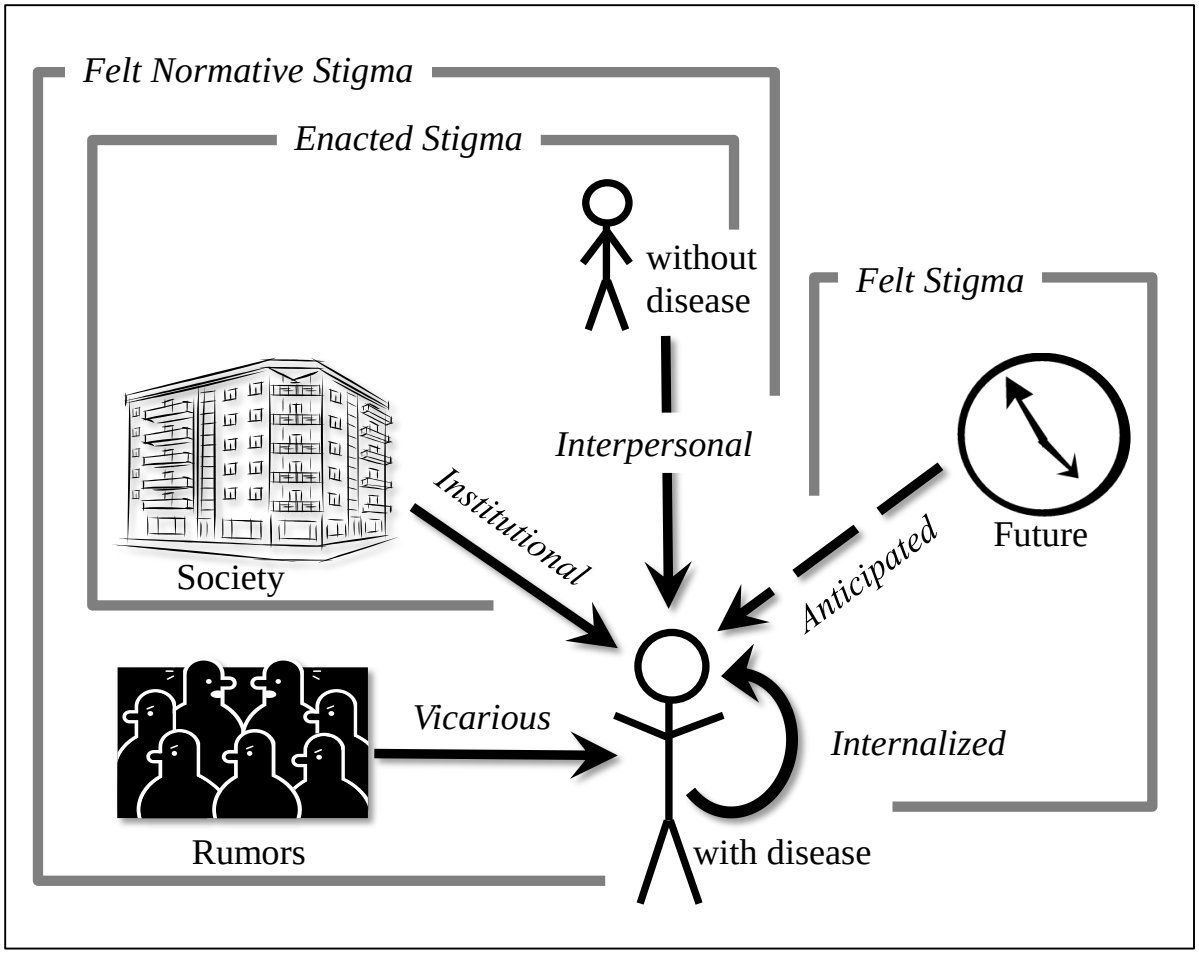


**Figure 1.1: Types of Disease-Associated Stigma**

between societies [52,71]. Individual characteristics associated with increased stigmatization are those related to power differentials in society; historically disadvantaged groups, such as women or racial and ethnic monitories, are often more adversely affected by stigma [52]. It has been proposed that the process of stigmatization has the same impact on population health as phenomena such as socioeconomic status and race [68,72]; however, it has not yet been awarded the same attention by public health officials. This is likely due to the challenges associated with quantifying stigma.

HIV and epilepsy are both highly stigmatized conditions and illustrate the substantial impact that disease- and individual-related characteristics have on the process of stigmatization as well as the impact that stigma has on the affected individual. Due to the substantial resources required and challenges encountered when conducting longitudinal studies, most of the research examining factors that contribute to or result from stigma are cross-sectional. The paucity of prospective data makes the directionality of stigma-associated factors unclear.

### *HIV-Related Stigma*

Since its identification in 1982 [73], HIV has been associated with considerable stigma [74,51]. Deemed one of the greatest obstacles to overcoming the HIV epidemic [75,76], stigmatizing beliefs associated with HIV have been shown to be greater than those associated with cancer [77,78], tuberculosis [79], Hepatitis C [80], and Severe Acute Respiratory Syndrome (SARS) [79]. Early work on HIV-related stigma in developed countries, where HIV was most prevalent among homosexual men and injection drug users, indicated that HIV adopted much of the stigma associated with these marginalized individuals [81,82]. As a result, it was initially believed in the United States and sub-Saharan Africa that HIV was associated with immoral behavior and affects individuals of low moral worth [83,84]. Compounded by a lack of cure and an often overstated high risk of transmission [85,86], HIV-positive individuals are often thought to be threatening to society [87,74,88-94,76].

In an attempt to design interventions to reduce HIV-related stigma, extensive research has examined the factors associated with stigma experienced by HIV-positive individuals. Identified factors can be divided into: factors that are associated with HIV progression; factors

that are specific to the individual; and factors related to the society in which the individual resides.

Greater stigma has been repeatedly associated with more advanced HIV infection, as assessed by lower $CD4^+$ T-cell count [95,96] and symptomatic disease [97,85,98-100]. However, multiple longitudinal studies have found that access to ARVs can both protect against [101-103] and be associated with [104,105] increased stigma. These conflicting findings are both related to concealment of infection [106]. Because visible signs of HIV infection increase the likelihood that one's HIV status will be disclosed against his wishes [85], ARVs may decrease the likelihood of disclosure by reducing identifiable signs of infection [107]. Conversely, ARVs may increase the likelihood of unintended disclosure due to drug side effects [108] as well as the need for regular medication and clinic attendance [109,110,105].

Individual-level characteristics associated with increased HIV-related stigma include: decreased access to resources – often measured by a lack of income [95] or employment [96] – decreased education [111-113], and decreased social support [100,114,115]. Access to resources may improve an individual's ability to conceal his HIV status, whereas education and social support may decrease the responsibility and blame that an individual acknowledges for his HIV status.

HIV-related stigma differs substantially between cultures [116,84,107]. Differences in beliefs about disease causality [93,117] and individual-level differences in social status influence stigma. These individual-level differences are frequently gender [75,118,119,100,111,120,121,113,122-124], age [111], sexual preference [85], and ethnicity [125,115]. In addition, societal structure affects stigmatization. HIV-positive individuals residing in societies where strong family and communal ties are a necessity for survival often

experience greater HIV-related stigma due to their inability, or perceived inability, to complete their assigned communal role [126,106,110].

The effect of HIV-related stigma is substantial. Among individuals who do not know their HIV status, HIV-related stigma decreases voluntary HIV testing [127,128,110,129-131]. Among HIV-positive individuals, stigma has been shown to decrease voluntary disclosure of HIV status [127,129,132-139] and increase social isolation [140,132,141,134,137] as well as decrease health care seeking behaviors [91,142,131,143] and ARV adherence [127,144-147,97,148,135,123,149,150]. Among, HIV-positive individuals, stigma has also been associated with decreased life satisfaction [151], decreased quality of life [152], and increased anxiety [153] and depression [134,95,97,154-159,148]. Recent research suggests that the adverse health effects associated with HIV-related stigma, such as depression, can persist even after the factors associated with stigma improve [95].

*Instruments*

Accurate assessment of HIV-related stigma is essential to both characterize the complexity of stigmatization and design interventions to decrease stigma [160,50]. Multiple instruments have been published to measure HIV-related stigma, both from the perspective of the unaffected public and HIV-positive individuals. Table 1.1 presents relevant information on instruments that have been validated to assess HIV-related stigma among HIV-positive people. Included are: the year the instrument was published; authors; name of scale; number of items and question response type; characteristics of the initial validation sample; the factors assessed by the scale, as characterized by the authors; and the aspects of stigma assessed, as characterized by the definitions previously provided.

**Table 1.1: Validated Instruments to Assess HIV-Related Stigma**

| Year | Authors | Title of Scale (Country) | Item Type | Validation Sample | Scale Factors (# of items) | Stigma Factors (# of Items) |
|---|---|---|---|---|---|---|
| 1997 | Sowell et al. [161] | Perception of Stigma of HIV$^+$ Women (United States) | 13 items, 4-point LT | 82 HIV$^+$ women | | Interpersonal (4)<br>Anticipated (7)<br>Internalized (2) |
| 2000 | Fife & Wright [77] | Social Impact Scale (United States) | 12 items, 4-point LT | 130 HIV$^+$ adults<br>76 adults with cancer | Social rejection (9)<br>Financial insecurity (3)<br>Internalized shame (5)<br>Social isolation (7) | Interpersonal<br><br>Felt<br>Internalized |
| 2001 | Berger et al. [162] | HIV Stigma Scale (United States) | 40 items, 4-point LT | 318 HIV$^+$ adults<br>81% men | Personalized stigma (18)<br>Disclosure concerns (10)<br>Negative self-image (13)<br>Concern with public attitudes about HIV (19) | Interpersonal<br>Anticipated<br>Internalized<br><br>Anticipated |
| 2002 | Lee et al. [163] | Internalized HIV Stigma (United States) | 2 items, dichotomous | 268 HIV$^+$ adults<br>65% men | Negative self-image (1)<br>Disclosure concerns (1) | Internalized<br>Anticipated |
| 2003 | Clark et al. [164] | Perceived Stigma Index 1 &2 (United States) | 4 items, dichotomous | 95 HIV$^+$ women<br>146 HIV$^-$ women (self-identified) | Perceived stigma | Interpersonal (1)<br>Anticipated (3) |
| 2003 | Reece [165] | HIV-Related Stigma[cd] (United States) | 11 items, 5-point LT | 132 HIV+ adults<br>68% men | | |

LT: Likert-type responses

[c] Based on Sowell et al.

[d] Individual items of scale not published

**Table 1.1 (cont'd)**

| Year | Authors | Title of Scale (Country) | Item Type | Validation Sample | Scale Factors (# of items) | Stigma Factors (# of items) |
|---|---|---|---|---|---|---|
| 2007 | Bunn et al. [166] | HIV Stigma Scale[e] (United States) | 32 items, 4-point LT | 157 HIV$^+$ adults >71% men | Enacted stigma (13)<br>Disclosure concerns (8)<br>Negative self-image (7)<br>Concern with public attitudes about HIV (6) | Interpersonal<br>Anticipated<br>Internalized<br><br>Anticipated |
| 2007 | Franke et al. [167] | HIV Stigma Scale[f] (Peru) | 14 items, 4-point LT | 130 HIV+ adults 46% men | Enacted stigma (5)<br>Disclosure concerns (5)<br>Negative self-image (6)<br>Concern with public attitudes about HIV (6) | Interpersonal<br>Anticipated<br>Internalized<br><br>Anticipated |
| 2007 | Holzamer et al. [133] | HIV/AIDS Stigma Instrument – PLWA (Lesotho, Malawi, South Africa, Swaziland, Tanzania) | 33 items, 4-point LT | 1,477 HIV+ adults 26% men | Verbal abuse (8)<br>Negative self-perception (5)<br>Health care neglect (7)<br>Social isolation (5)<br>Fear of contagion (6) | Interpersonal<br><br>Internalized<br>Interpersonal<br>Interpersonal<br>Interpersonal |
| 2007 | Wright et al. [168] | HIV Stigma Scale[g] (United States) | 10 items, 5-point LT | 64 HIV$^+$ youth 52% men | Workplace stigma (2)<br>Disclosure concerns (2)<br>Negative self-image (3)<br>Concern with public attitudes about HIV (2) | Interpersonal<br>Anticipated<br>Internalized<br><br>Anticipated |

LT: Likert-type responses

[e] Based on Berger et al.

[f] Based on Berger et al.

[g] Based on Berger et al.

**Table 1.1 (cont'd)**

| Year | Authors | Title of Scale (Country) | Item Type | Validation Sample | Scale Factors (# of items) | Stigma Factors (# of items) |
|---|---|---|---|---|---|---|
| 2008 | Sayles et al. [169] | Internalized HIV Stigma Scale (United States) | 28 items, 5-point LT | 202 $HIV^+$ adults<br>50% men | Stereotypes (12)<br>Disclosure concerns (5)<br>Social relationships (7)<br>Self-acceptance (4) | Interpersonal<br>Anticipated<br>Interpersonal<br>Internalized |
| 2008 | Van Rie et al. [170] | HIV/AIDS Stigma Scale (Thailand) | 22 items, 4-point LT | 480 Tuberculosis patients<br>22% $HIV^+$<br>66% men | Community perspectives toward HIV/AIDS (11)<br>Patient perspectives toward HIV/AIDS (10) | |
| 2008 | Visser et al. [171] | Internalized Stigma Scale (South Africa) | 12 items, Dichotomous | 317 $HIV^+$ women | Blame and judgment (6)<br>Interpersonal distancing (6) | Internalized<br><br>Anticipated |
| 2009 | Kalichman et al. [172] | Internalized AIDS-Related Stigma Scale (South Africa, Swaziland, United States) | 6 items, Dichotomous | 2,397 $HIV^+$ adults<br>41% men | Negative self-perception | Internalized |
| 2010 | Jimenez et al. [173] | HIV Felt Stigma Scale[h] (Puerto Rico) | 17 items, 4-point LT | 216 $HIV^+$ adults | Personalized stigma (5)<br>Disclosure concerns (4)<br>Negative self-image (5)<br>Concern with public attitudes (3) | Interpersonal<br>Anticipated<br>Internalized<br><br>Interpersonal |
| 2011 | Birbeck et al. [174] | Jacoby's Stigma Scale (Zambia) | 3 items, Dichotomous | 496 $HIV^+$ adults<br>41% men | | Interpersonal |

LT: Likert-type responses

[h] Based on Berger et al.

**Table 1.1 (cont'd)**

| Year | Authors | Title of Scale (Country) | Item Type | Validation Sample | Scale Factors (# of items) | Stigma Factors (# of items) |
|---|---|---|---|---|---|---|
| 2012 | Zelea et al. [175] | HIV/AIDS Stigma Scale (India) | 22 items, 4-point LT | 188 $HIV^+$ adults 41% men | Self-stigma (8)<br>Experienced stigma (7)<br>Perceived stigma (8) | Felt<br>Interpersonal<br>Anticipated |
| 2013 | Jeyaseelan et al. [176] | HIV Stigma Scale[i] (India) | 25 items, 4-point LT | 250 $HIV^+$ adults 50% men | Personalized stigma (11)<br>Disclosure concerns (4)<br>Negative self-image (6)<br>Concern with public attitudes about HIV (4) | Interpersonal<br>Anticipated<br>Internalized<br><br>Anticipated |
| 2013 | Kingori et al. [177] | HIV Felt Stigma Questionnaire[j] (Kenya) | 18 items, 5-point LT | 370 $HIV^+$ adults | Public attitudes (3)<br><br><br>Ostracize (3)<br>Discrimination (2)<br>Personal life disrupted (2) | Interpersonal, Anticipated, & Internalized<br>Interpersonal<br>Interpersonal<br><br>Interpersonal |
| 2013 | Tsai et al. [178] | Internalized AIDS-Related Stigma Scale[k] (Uganda) | 6 items, Dichotomous | 456 $HIV^+$ adults 31% men | Negative self-perception | Internalized |

LT: Likert-type responses

[i] Based on Berger et al.

[j] Based on Reece

[k] Based on Kalichman et al.

Because stigma is a culturally-specific construct [107], it is critical that instruments to measure HIV-related stigma are valid for the population assessed. Most of the instruments for HIV-related stigma have been developed and validated in the United States. Only five have been validated in sub-Saharan Africa, where most HIV-positive individuals reside. The Berger HIV Stigma Scale is arguably the most frequently utilized HIV-related stigma measure; it has been shortened and validated both in the United States [166,168], Puerto Rico [173], Peru [167], and India [176]. The factors assessed by Berger et al.'s original scale correspond well to enacted, anticipated, and internalized stigma [162]. Unfortunately, validation data for the HIV Stigma Scale has not been published for sub-Saharan Africa. In addition, only two of the forty items can be found in all of the validated versions of the HIV Stigma Scale, which suggests that the cross-cultural validity of this instrument may need to be re-evaluated.

The HIV/AIDS Stigma Instrument – PLWA (HASI-P), published in 2007 by Holzamer et al., was developed and validated with 1,477 HIV-positive adults residing in five sub-Saharan African countries [133]. The cultural diversity between and within the research sites suggest that this instrument may be well equipped to assess culture-relevant manifestations of HIV-related stigma in sub-Saharan Africa. The authors grouped items into six categories: verbal abuse; healthcare neglect; social isolation; fear of contagion; workplace stigma; and negative self-perception. The first four categories assess interpersonal stigma, whereas negative self-perception assesses internalized stigma. One question under fear of contagion ("I stopped eating with other people") may assess anticipated stigma, although this requires further investigation.

Other HIV-related stigma measures for use in HIV-positive individuals in sub-Saharan Africa include: the Jacoby Stigma Scale, the Internalized AIDS-Related Stigma Scale, and the HIV Felt Stigma Questionnaire. The Jacoby Stigma Scale is an adaptation of a stigma

instrument frequently used with epilepsy [179] and has been used in Zambia to assess interpersonal stigma [180]. The Internalized AIDS-Related Stigma Scale is a six-item instrument with dichotomous answers that was validated in South Africa, Swaziland, and the United States to assess internalized stigma [172]. It has since been validated in rural Uganda [178]. The HIV Felt Stigma Questionnaire is based on a previous instrument used in the United States [165] and is primarily a measure of enacted stigma.

***Epilepsy-Associated Stigma***

The etiology of epilepsy is subject to numerous misconceptions worldwide that perpetuate disease-associated stigma, such as associations with supernatural causes and taboo behaviors [181-186,71,187]. Multi-nation surveys suggest that epilepsy-associated stigma is a widely prevalent social phenomenon [188-190]. Like HIV-related stigma, the factors that influence the development of epilepsy-associated stigma among people with epilepsy can be divided into: factors specific to the condition; factors related to the individual; and factors specific to the society in which the individual resides.

More severe epilepsy, often assessed by frequency or type of seizure, has been repeatedly associated with greater stigma [191,179,62,192-194,188,195,187,196-199,54] as has duration of disease [193,188,195,200,62]. Although the use of AEDs to control seizures is associated with decreased stigma [195], polytherapy [201], ineffective treatment [185,202], and drug side effects [189,187,198] are associated with increased stigma. These condition-specific factors all increase stigma by decreasing the likelihood of concealment for people with epilepsy.

Individual-specific factors associated with increased stigma that may result in decreased concealment include: earlier age of onset [193,197,198,203,199]; decreased resources, as

assessed by socioeconomic status and employment [204,195,62,197,185,205]; and seizure-related injuries, such as broken bones and burns [189,196]. Individual factors that may increase stigma due to increased responsibility for epilepsy include: less formal education [192,196,62,197,205-207]; less epilepsy-related knowledge [188,185,184,66]; lower self-efficacy [208,189,62,197,198]; and poor coping related to epilepsy [209,210,198]. Decreased social support has also been associated with increased epilepsy-associated stigma [195,62,211,54,212,213], although the directionality of this relationship is unclear. An individual's social status also impacts epilepsy-associated stigma [71]. Common society-level factors associated with increased stigma are gender [192] and race [197].

People with epilepsy often suffer considerable social rejection due to epilepsy-associated stigma [55,214-216,196,54,217,207]. This has far-reaching effects, such as lower self-esteem [66,54,196] and decreased health-related quality of life [218-221,196,222,200,223,198,185,224,202]. Individuals who report higher levels of epilepsy-related stigma are also more likely to experience anxiety [196,212,225,226] and depression [227,196,228,229,213,230,225] than those with lower levels of stigma. People with higher levels of epilepsy-associated stigma also have decreased AED adherence [231].

*Instruments*

Compared to HIV-related stigma, relatively few instruments have been developed to assess epilepsy-associated stigma. Table 1.2 provides details regarding the instruments that have been validated to assess epilepsy-associated stigma. Of the eleven published, only two were developed in low-income countries.

**Table 1.2: Validated Instruments to Assess Epilepsy-Associated Stigma**

| Year | Authors | Title of Scale (Country) | Item Type | Validation Sample[l] | Scale Factors (# of items) | Stigma Factors (# of items) |
|---|---|---|---|---|---|---|
| 1980 | Ryan et al. [192] | Perceived Stigma Scale (United States) | 6 items, Dichotomous | 445 adults 51% men | Perceived stigma | Interpersonal |
| 1992 | Jacoby [179] | Stigma Scale (United Kingdom) | 3 items, Dichotomous | 139 adults 45% men | | Interpersonal |
| 1992 | Westbrook et al. [66] | Perceived Stigma Scale (United States) | 4 items, 4-point LT | 64 children 39% boys | Perceived stigma | |
| 1993 | Austin & Huberty [232] | Child Attitude Toward Illness Scale (United States) | 13 items, 4-point LT | 136 children 133 children with asthma | Attitude | Internalized |
| 2003 | DiIorio et al. [62] | Parent Stigma Scale, adapted for adults with epilepsy[m] (United States) | 10 items, 7-point LT | 314 adults 50% men | | |
| 2004 | Austin et al. [63] | Child Stigma Scale (United States) | 8 items, 5-point LT | 224 children 48% boys | | Internalized (2) Interpersonal (4) Anticipated (2) |

LT: Likert-type responses

[l] All validation samples are people with epilepsy unless otherwise noted

[m] Based on Austin & Huberty

**Table 1.2 (cont'd)**

| Year | Authors | Title of Scale (Country) | Item Type | Validation Sample[n] | Scale Factors (# of items) | Stigma Factors (# of items) |
|---|---|---|---|---|---|---|
| 2007 | Fernandes et al. [233] | Stigma Scale of Epilepsy (Brazil) | 24 items, 4-point LT | 40 adults<br>40 adults without epilepsy | | Anticipated (17)<br>Internalized (7) |
| 2010 | Prus & Grant [234] | Stigma of Epilepsy Scale (United States) | 5 items, Dichotomous | 109 adults<br>40% men | | Internalized (2)<br>Anticipated (1)<br>Interpersonal (1) |
| 2012 | Mbuba et al. [203] | Kilifi Stigma Scale of Epilepsy (Kenya) | 18 items, 3-point LT | 203 adults<br>40 caregivers of children with epilepsy | Perceived stigma | Internalized (7) |
| 2013 | Forsgren et al. [235] | Internalized Stigma of Mental Illness Scale, adapted for Epilepsy (Sweden, Iran) | 29 items, 4-point LT | 230 adults | Alienation<br>Stereotype endorsement<br>Perceived discrimination<br>Social withdrawal<br>Stigma resistance | Internalized<br><br>Interpersonal<br>Anticipated<br>Anticipated |

LT: Likert-type responses

[n] All validation samples are people with epilepsy unless otherwise noted

The most widely used instrument to assess epilepsy-associated stigma is Jacoby's Stigma Scale [179]. Modified from an instrument used to assess stigma associated with stroke [236], it has been used worldwide to gauge interpersonal stigma among people with epilepsy [189,194,185,195,54,229,237,198]. However, as epilepsy-associated stigma consists of more than interpersonal stigma, an instrument that can also assess internalized and anticipated stigma among people with epilepsy is essential. In addition, because epilepsy-associated stigma is a result of interactions between individuals with and without epilepsy, an instrument that could be used with both involved parties would greatly enhance our understanding of disease-associated stigma.

The Stigma Scale of Epilepsy (SSE) was developed in Brazil to assess felt stigma when administered to people with epilepsy and to assess stigmatizing attitudes that may lead to discrimination and prejudice when administered to the general public [233]. Unlike previous attempts to measure felt stigma and stigmatizing beliefs that involved the use of two separate, yet parallel worded instruments, the SSE asks the same questions to the general public and people with epilepsy. Previous research suggests that querying an individual with epilepsy about how "people with epilepsy" feel, instead of how "you" feel, results in the participant being more likely to provide a response more closely related to his true attitude [238]. The SSE has been used in India [200] and Bolivia [239] and may be a valuable tool to understand the interactions that lead to the development of epilepsy-associated stigma if validated more widely.

The Kilifi Stigma Scale is the only instrument developed and validated in sub-Saharan Africa. This 18-item instrument was designed to assess perceived stigma among people with epilepsy in Kenya. Interestingly, none of the items mention epilepsy, therefore, it is unclear if participant responses can be directly attributed to internalized stigma [240]. In addition, since

two-thirds of the validation sample consisted of caretakers of people with epilepsy, the instrument may more accurately reflect stigmatization resulting from proximity to a condition (*affiliate stigma*) versus felt stigma [241,63].

### *Comorbid, Layered Stigma*

It is widely acknowledged that HIV-positive individuals are often subject to multiple stigmatized conditions simultaneously [242,243,81]. The limited research examining double [244] or layered stigma [81] characterizes stigma that develops in the setting of a pre-existing negative social identity [48] and has primarily focused on behaviors associated with HIV transmission, such as injection drug use [243], or individual characteristics, such as being a member of a racial minority [242] or having a different sexual orientation [244]. These studies suggest that layered stigma alters an individual's exposure to enacted stigma and influences felt stigma [242,80].

Only three published studies have examined layered stigma resulting from comorbid medical conditions. Lekas et al. conducted qualitative interviews to examine enacted and felt stigma among patients co-infected with HIV and Hepatitis C in New York City [80]. Most participants reported that stigmatization associated with HIV was more intense than that associated with Hepatitis C, yet some suggested that they were equally stigmatized due to their association with injection drug use [80]. Participants found that by concealing their Hepatitis C status, they could reduce experiences of enacted stigma [80]. Deribew et al. noted that individuals with HIV and Tuberculosis (TB) reported greater HIV-related stigma, as assessed by the Berger HIV Stigma Scale in Ethiopia [245]. All TB/HIV co-infected participants were interviewed just after their TB diagnosis, therefore, their experiences may more accurately reflect

heightened HIV-related stigma due to TB's association with HIV [246] rather than layered stigma. Lastly, Walkup et al. examined layered enacted stigma associated with HIV and schizophrenia by presenting vignettes to members of the general public (college undergraduate students) [247]. The authors found that the stigma associated with HIV and schizophrenia was additive, but not significantly different from the stigma associated with either condition in isolation [247].

There is a lack of quantitative data on layered stigma from the perspective of people with comorbid conditions. This may be due to a lack of valid measurements. Although instruments have been designed to assess disease-associated stigma across conditions [248,249], none have been constructed to detect comorbid layered stigma. It is unclear if existing disease-specific instruments have sufficient sensitivity to detect layered stigma. Investigation into this type of layered stigma is warranted as it may adversely affect health outcomes, such as depression and medication adherence, and could adversely affect the medical management of both conditions.

**Medical Management of HIV**

Four years after first isolating HIV from immunocompromised patients [250], zidovudine (AZT) was approved by the Food and Drug Administration (FDA) to treat HIV-positive individuals [251]. Although AZT improved survival among AIDS patients [252], the development of significant drug toxicity and HIV viral strains resistant to AZT led clinicians to treat patients with multiple ARVs simultaneously [253,254]. Today, HIV is managed with combination antiretroviral therapy (cART), which consists of at least three ARVs acting via different mechanisms to inhibit the replication of HIV [255]. To date, there are 28 ARVs available that can be divided into six different classes based on mechanism of action [256].

Table 1.3 lists the most widely used HIV drugs as well as the following details: the year granted FDA approval; main mechanism of in-vivo drug metabolism; effect on liver enzymes, including the Cytochrome P450 enzyme system (CYP450); and common adverse events.

The primary aim of cART is to suppress HIV viral replication in order to slow disease progression and permit immune reconstitution, while minimizing drug associated adverse events [257]. Secondary aims include limiting the development of ARV resistance in HIV strains [257] and decreasing HIV transmission [255]. To accomplish these goals, the WHO has recommended "first line" cART for HIV-positive individuals initiating treatment for the first time and "second line" for those who do not achieve or maintain HIV viral suppression on first line therapy (*ARV treatment failure*) [255]. Table 1.4 provides the latest WHO recommendations for first and second line cART [255]. These drug combinations are being made available at low or no cost for HIV-positive individuals worldwide via government funding and substantial international aid [9].

The WHO acknowledges, and research has repeatedly shown, that sustained adherence to cART is essential in order to decrease HIV replication so that plasma HIV viral load becomes undetectable [255,258-261]. Although the WHO emphasizes adherence but does not offer guidelines on the extent to which adherence is required, studies suggest that HIV-positive individuals taking their medications as prescribed more than 90% of the time are less likely to experience treatment failure than those with less than 90% adherence [262,261,263]. Substantial research has examined barriers to adherence and shown that ARV-associated adverse events often lead to decreased adherence [264-268,149]. Compared to other medications, short-term ARV-related side effects have been relatively well studied [256]. Unfortunately, they are often

**Table 1.3: Common Adverse Events Associated with HIV Medications**

| Drug | FDA Approval [251] | In-Vivo Metabolism | Enzyme Effects | Adverse Events |
|---|---|---|---|---|
| *Nucleoside Reverse-Transcriptase Inhibitors (NRTIs)* | | | | |
| Zidovudine (AZT) | 1987 [269] | UGTs [269] | None | Nausea/Vomiting [270,271], Lipodystrophy [272], Leuokopenia [270], Anemia [270,273], Neutropenia [269] Fatigue/Malaise [271,269], Myopathy [273], Rash [274], Lactic Acidosis [269]. |
| Didanosine (ddI) | 1991 [275] | Renal [275] | None | Nausea [274,276], Lipodystrophy [272], Peripheral neuropathy [273], Pancreatitis [274,275], Lactic acidosis [274], Optic neuritis [275]. |
| Stavudine (D4T) | 1994 [277] | Renal [277] | None [277] | Nausea [270], Peripheral neuropathy [278,270,273], Lipodystrophy [272,278], Hypertriglyceridemia [270,279], Lactic acidosis [274,277], Headache [279], Hypercholesterolemia [279], Diarrhea [277]. |
| Lamivudine (3TC) | 1995 [280] | Renal [280] | None | Nausea [270], Peripheral neuropathy [270], Hypertriglyceridemia [270], Lipodystrophy [270,281], Pancreatitis [282], Mood alterations [279]. |
| Abacavir (ABC) | 1998 [283] | UGTs | None [283] | Hypersensitivity rash [273,274,283], Vomiting [279], Immune reconstitution syndrome [283], Lipodystrophy [283]. |
| Tenofovir (TDF) | 2001 [284] | Renal [284] | None [284] | Rash [284], Diarrhea [284], Headache [284], Renal insufficiency [274,285]. |
| Emtricitabine (FTC) | 2003 [286] | Renal [286] | None [286] | Headache [286], Diarrhea [286], Nausea [286], Rash [286], Skin discoloration (rare) [287]. |
| *Non-Nucleoside Reverse-Transcriptase Inhibitors (NNRTIs)* | | | | |
| Nevirapine (NVP) | 199 6[288] | CYP3A, CYP2B6 [288] | Induces CYP3A, CYP2B6 [288] | Hypersensitivity [289], Rash [273,274], Hepatotoxicity [290,279]. |

CYP: Cytochrome P450 Enzyme; UGT: UDP-Glucuronosyltransferase System

**Table 1.3 (cont'd)**

| Drug | FDA Approval [251] | In-Vivo Metabolism | Enzyme effects | Adverse Events |
|---|---|---|---|---|
| *Non-Nucleoside Reverse-Transcriptase Inhibitors (NNRTIs) cont'd* | | | | |
| Efavirenz (EFV) | 1998 [291] | CYP3A, CYP2B6 [291] | Induce CYP3A, CYP2B6 [291] | Hypersensitivity rash [273], Dizziness [273,274], Insomnia [273], Somnolence [273], Vivid dreams [273,274], Depression [291] Hypertriglyceridemia [274], Unsteady walking [274], Drowsiness [274], Mood alterations [279]. |
| *Protease Inhibitors (PIs)* | | | | |
| Lopinvir ritonavir (LPV/r) | 2000 [292] | CYP3A | Inhibits CYP3A | Diarrhea [293,294], Hypertriglyceridemia [293], Hypercholesterolemia [294], Nausea [294], Paresthesia [273], Pancreatitis [292], Hepatotoxicity [292], Cardiac Conduction Abnormalities [292]. |
| Atazanavir/ ritonavir (ATV/r) | 2003 [295] | CYP3A [295] | Inhibits CYP3A, CYP2C8 [295] | Jaundice [294,274], Paresthesia [273], Hyperbilirubinemia [276], Cardiac Conduction Abnormalities [295], Rash [295], Hyperbilirubinemia [295]. |

CYP: Cytochrome P450 Enzyme

underreported in routine clinical settings [296,297]. To ensure sustained cART adherence with the underlying goal of promoting individual health and decreasing HIV transmission, it is essential to continually assess for and appropriately manage ARV-associated side effects.

**Table 1.4: WHO Recommended cART Combinations**

| Line | cART Combination |
|---|---|
| *First line* | |
| Preferred | TDF + 3TC (or FTC) + EFV |
| Alternatives | AZT + 3TC + EFV<br>AZT + 3TC + NVP<br>TDF + 3TC (or FTC) + NVP |
| *Second line* | |
| If D4T or AZT was first line | TDF + 3TC (or FTC) + ATV/r or LPV/r |
| If TDF was first-line | AZT+ 3TC + ATV/r or LPV/r |

**Medical Management of Epilepsy**

More than twenty drugs are available to manage epilepsy [298]. AEDs prevent seizures by acting via multiple, incompletely understood mechanisms to inhibit abnormal neuron depolarization in the brain [298,299]. AEDs are divided into generations, based on when they were identified. Table 1.5 lists the AEDs that are considered first-line by the WHO [25,300]. All are first generation AEDs and were selected both for their efficacy as well as their cost [301]. Also provided are: the year each AED was approved; primary mechanism of in-vivo metabolism; effect on liver enzymes; and common adverse events. Although these drugs are considered essential medicines by the WHO, they are often unavailable in low and middle income countries [27,302,25,303].

For AEDs to effectively control seizures, there must be an adequate concentration of the drug in the blood. This requires continuous medication adherence [304,32,33,305]. As has been found in individuals treated with cART, people experiencing AED-associated adverse

**Table 1.5: Common Adverse Events Associated with First-Generation AEDs.**

| Drug | FDA Approval [251] | In-Vivo Metabolism | Enzyme Effects | Adverse Events |
|---|---|---|---|---|
| Phenobarbital (PB) | Pre-1938 [251] | CYP2C9 [306] | Induces CYP2C9, CYP2C19, CYP3A4, UGTs [306] | Anemia [307], Sedation [308,309], Rash [309], Depression [309], Hyperactivity [310], Dizziness [311]. |
| Carbamazepine (CBZ) | 1968 [312] | CYP1A2 (minor) [306], CYP3A4 [312,306] | Induces CYP2C9, CYP2C19, CYP3A4, UGTs [312,306] | Rash [313,312], Psychomotor Performance [314], Asterixis [315], Ataxia [316], Blurred Vision [310], Anemia [312], Dizziness [312]. |
| Phenytoin (PHT) | 1956 [317] | CYP2C9, CYP2C19 [306] | Induces CYP3A4, CYP2C19 | Anemia [307], Hypocalcemia [307], Impaired Memory [314], Gum Hypertrophy [316], Rash [316], Nystagmus [310]. |
| Valproic Acid (VA) | 1996 [318] | UGTs [318,306], CYP2C9 (minor) [306] | Inhibits UGT [319,306], possibly CYP2C9 [306] | Nausea/Vomiting [310], Tremor [310], Hepatoxocity [318], Abdominal pain [318], Blurred Vision [318], Ataxia [318], Somnolence [318], Change in Weight [318], Headache [318], Dizziness [318]. |

CYP: Cytochrome P450 Enzyme; UGT: UDP-Glucuronosyltransferase System

events are less like to adhere to their prescribed medication [231,320-322]. AED side effects are a frequently cited cause for changing or discontinuing treatment [323-326]. Although short- and long-term adverse events associated with first-line AEDs are relatively well understood [321], the high prevalence of adverse events associated with these drugs in high-income countries have not been reported in low-income countries [327-331]. This may be because the studies reporting side effects in low-income settings often have the primary purpose of decreasing the epilepsy treatment gap by providing AEDs to people not already obtaining care [331,332,328,330]. It has been repeatedly shown that patients are more likely to tolerate side effects when they believe the

medication is somewhat efficacious and alternative therapies unavailable [333-335]. In addition, data are lacking about adverse events experienced by people taking first-generation AEDs with other, more recently developed medications in low-income countries. As three first-generation AEDs have substantial effects on enzymes responsible for metabolizing other medications [306], this could be cause for serious concern [336]. Therefore, additional research examining patient-reported adverse events to AEDs is necessary, particularly in low-income countries.

**Managing Comorbid HIV and Epilepsy**

CYP450 enzymes are responsible for the breakdown of about 80% of modern medications [336]. Found throughout the body, but most prominently in the liver, the pharmacokinetic activity of CYP450 enzymes can be induced and inhibited by a variety of drugs and other substances [337,336,306]. Enzyme induction occurs when an inducer, such as a drug, binds to an intracellular receptor and causes increased transcription of CYP450 genes [336]. This results in the production of additional CYP450 enzymes and increases plasma clearance of drugs by that specific enzyme [336]. Depending on the concentration of the drug remaining after induction, CYP450 induction could result in both decreased efficacy of prescribed drugs and unpredictable side effects [306,336]. The extent of enzyme induction depends on the concentration of the inducer, the potency of the inducer (i.e. to what extent it induces CYP450 replication), and characteristics of the individual [338]. Enzyme induction begins as soon as the offending medications are combined, but that maximum induction occurs when the inducer

reaches its steady state concentration, which occurs after four to five half-lives[o] [306]. Thus the clinical effect of enzyme induction could appear days to weeks after medication co-administration begins [306,339]. De-induction also occurs when the inducer is stopped and, if halted suddenly, can lead to drug toxicity [306,340,341]. Enzyme inhibition, on the other hand, blocks CYP450 activity and decreases the clearance of drugs broken down by that enzyme [306]. Like induction, the extent of enzyme inhibition depends on the concentration and characteristics of the inhibitor as well as the characteristics of the individual [306].

CYP450 enzyme activity alterations have been repeatedly documented after the administration of the following enzyme-inducing AEDs (EI-AEDs): phenobarbital (PB), carbamazepine (CBZ), and phenytoin (PHT) [306,339,301,342-344] as well as after administration of the following ARVs: nevirapine (NVP), efavirenz (EFV), lopinavir/ritonavir (LPV/r), and atazanavir/ritonavir (ATV/r) [345-351]. However, data on *in-vivo* interactions are limited. Table 1.6 summarizes the published pharmacokinetic data available on these interactions. For ethical reasons, some of these studies were conducted in healthy adults [352,353,348] and may not be representative of pharmacokinetic interactions in HIV-positive individuals due to HIV's detrimental effect on the liver [354].

Although pharmacokinetic data is scant, there are significant clinical implications for interactions between ARVs and EI-AEDs. Data from a cohort of HIV-positive individuals in the United States military on concurrent treatment suggest that EI-AEDs substantially decrease the

[o] A half-life is the amount of time that it takes for half of the drug to be metabolized. It depends on the concentration of the drug, its metabolites, and the activity of the enzymes responsible for its metabolism.

**Table 1.6: Pharmacokinetic Interactions between First-Generation AEDs and ARVs.**

| Drug Interaction | Study Population | Methods | Outcomes | Findings |
|---|---|---|---|---|
| Phenobarbital (PB) & Nevirapine (NVP) | HIV-negative, non-pregnant white Dutch women [352] | SD-NVP, 200mg +SD-PB, 200mg simultaneously | $t_{½}$ of NVP | PB ↔ $t_{½}$ NVP |
| Carbamazepine (CBZ) & Nevirapine (NVP) | HIV-negative, non-pregnant white Dutch women [352] | SD-NVP, 200 mg+ SD-PB, 400mg simultaneously | $t_{½}$ of NVP | CBZ ↓ $t_{½}$ NVP |
| Carbamazepine (CBZ) & Efavirenz (EFV) | 12 healthy volunteers [353] | 21 days of CBZ titrated to 400mg OD, 13 days of SD-CBZ, 400mg+SD-EFV, 600mg | [EFV] | CBZ ↓ [EFV] |
| | 14 healthy volunteers [353] | 14 days of SD-EFV, 600mg, 20 days SD-EFV 600mg+SD-CBZ, 400mg | [CBZ] | EFV ↓ [CBZ] |
| Phenytoin (PHT) & Nevirapine (NVP) | HIV-negative, non-pregnant white Dutch women [352] | SD-NVP, 200 mg+ SD-PHT, 184mg simultaneously | $t_{½}$ of NVP | PHT ↔ $t_{½}$ NVP |
| | HIV-negative, non-pregnant white Dutch women [352] | SD-NVP, 200 mg+ SD-PHT, 184mg simultaneously, plus SD-PHT, 184mg OD for 2 days | $t_{½}$ of NVP | PHT ↓ $t_{½}$ NVP |
| | HIV-negative, non-pregnant white Dutch women [352] | SD-NVP, 200 mg+ SD-PHT, 184mg simultaneously, plus SD-PHT, 184mg OD for 6 days | $t_{½}$ of NVP | PHT ↓ $t_{½}$ NVP |
| Phenytoin (PHT) & Lopinavir/ritonavir (LPV/r) | 12 healthy volunteers [348] | LPV/r 400/100mg BD for 10 days, LPV/r 400/100mg BD+PHT 300mg OD for 11days | [LPV/r] | PHT ↓ [LPV/r] |
| | 12 healthy volunteers [348] | PHT 300mg OD for 11 days, PHT 300mg OD +LPV/r 400/100mg BD for 11days | [PHT] | LPV/r ↓ [PHT] |
| Valproic Acid (VA) & Efavirenz (EFV) | 11 HIV-positive American adults [351] | Stable taking 600 mg OD EFV, added VA, time not specified | [EFV] | VA ↔ [EFV] |
| Valproic Acid (VA) & Lopinvair/ritonavir (LPV/r) | 11 HIV-positive American adults [351] | Stable taking 400/100 mg BD LPV/r, added VA, time not specified | [LPV/r] | VA ↑ [LPV/r] |

SD: single dose; ↔: no effect; ↓: decrease; ↑: increase; [X]: plasma concentration of X; $t_{½}$: half-life; OD: once daily

plasma concentration of ARVs [355] and may lead to ARV treatment failure [356]. This has led to recommendations that clinicians proceed cautiously when prescribing AEDs to HIV-positive individuals [353]. Health care providers are advised to either prescribe AEDs that are not enzyme-inducing or monitor plasma concentrations of ARVs if an EI-AED must be used [353,336]. Unfortunately, in resource-limited settings where alternative AEDs are limited [357,358] and pharmacokinetic monitoring may be unavailable, providers often have no alternative but to prescribe therapies that may result in adverse outcomes. Until additional clinical data confirms the adverse effects of combining EI-AEDs with first and second-line ARVs, there is little impetus for the international community to prioritize providing costly alternative AEDs in low-income settings.

## STUDY RATIONALE

Ample opportunity is available for HIV and epilepsy to co-occur, especially in sub-Saharan Africa, where the prevalence of both conditions is high. Individuals most likely to be affected by HIV and epilepsy in this setting are young and may be forced to cope with substantial social and medical morbidity for most of their lives.

Both HIV and epilepsy are highly stigmatized conditions. The stigma associated with either condition in isolation has been shown to have widespread effects that linger even after physical health improves. The assessment of stigma, especially epilepsy-associated stigma, is complicated by the lack of widely validated instruments that adequately capture all aspects of this sociocultural phenomenon. In addition, little is known about the layered stigma that results in individuals with HIV and epilepsy or what effect layered stigma may have on health outcomes commonly seen among stigmatized individuals, such as anxiety and depression.

Both HIV and epilepsy can be managed with long-term therapy. However, both conditions require strict adherence to medications associated with side effects. Pharmacokinetic data suggests - and limited clinical data has confirmed – that adverse events would likely be associated with co-treatment with cART and EI-AEDs. Patients taking cART and EI-AEDs together could experience unpredictable side effects, recurrent seizures, uncontrolled HIV viral replication, and the development of ARV resistance leading to treatment failure. Adverse events resulting from concurrent cART and EI-AED treatment threaten both individual and population heath by increasing the risk of death for people with HIV and epilepsy and increasing the likelihood of transmission of HIV viral resistance to others. Unfortunately, sparse clinical data exist regarding this interaction from sub-Saharan Africa, where alternative treatment for HIV and epilepsy is currently not feasible.

The social and medical morbidity of HIV and epilepsy are interrelated. HIV-related and epilepsy-associated stigma both increase with the severity of disease, pill burden, and medication side effects. Co-treatment for HIV and epilepsy requires multiple medications and may result in adverse events that exacerbate disease severity. Stigma often leads to anxiety and depression as well as to decreased medication adherence. Prior research has shown that increased anxiety and depression are related to higher perception of drug-related adverse events [359] and that adverse events are associated with decreased medication adherence, which exacerbates disease severity. At the population level, both HIV and epilepsy are associated with significant social and economic costs that could be mitigated by improved management [360,361,5,362,18,110,363].

To mitigate the long-term effects of comorbid HIV and epilepsy, the medical and social burden of these conditions must first be adequately characterized in a setting where the implications of comorbid HIV and epilepsy may be most serious like sub-Saharan Africa

## OBJECTIVES

To examine the social intersection of HIV and epilepsy by:

1. Validating the Stigma Scale of Epilepsy (SSE) for use with Zambian people with epilepsy using data collected in 2009.
2. Comparing epilepsy-associated and HIV-related stigma reported by: people with comorbid HIV and epilepsy; people with epilepsy only, and people with HIV only in Zambia. Psychiatric morbidity will also be examined.

To examine the medical intersection of HIV and epilepsy:

1. Assessing adverse events associated with the EI-AED phenobarbital among Zambian people with epilepsy.
2. Comparing the severity of adverse events experienced by an inception cohort of HIV-positive individuals on therapy with both an EI-AED plus ARVs in comparison to HIV-positive individuals taking ARVs alone and HIV-positive individuals taking neither an EI-AED nor ARVs.

## CHAPTER TWO:

## VALIDATION OF THE STIGMA SCALE OF EPILEPSY IN ZAMBIA


### Abstract

*Objective*

Epilepsy-associated stigma is an important patient-centered outcome measure, yet quantifying stigma remains challenging. The instrument commonly used to assess felt stigma among people with epilepsy is Jacoby's 3-item Stigma Scale. However, due to noted ceiling effects, attempts to develop other felt stigma measures were undertaken. The Brazilian Stigma Scale of Epilepsy (SSE) is a 24-item instrument that was designed to measure felt stigma among people with epilepsy and stigmatizing attitudes when administered to others. If cross-culturally valid, this tool may overcome concerns associated with Jacoby's 3-item Stigma Scale, elucidate determinants of stigma, and provide an outcome measure for stigma reduction interventions.

*Methods*

We assessed the measurement properties of the SSE in 102 Zambian people with epilepsy. Using Item Response Theory, we examined the number of underlying latent traits assessed by the SSE. We also conducted a confirmatory factor analysis to compare the latent traits assessed by the SSE to the latent traits assessed by Jacoby's 3-item Stigma Scale. Differential item functioning based on forced disclosure of epilepsy status was also examined.

*Results*

The SSE loaded onto two latent traits related to stigma – the first included questions regarding difficulties and prejudices faced by people with epilepsy, whereas the second loaded questions regarding emotions associated with epilepsy. Items from Jacoby's 3-item Stigma Scale loaded only onto the first factor, suggesting that it does not assess the second. Forced disclosure of epilepsy increased worry and pity - items associated with the second factor.

*Conclusion*

In Zambian people with epilepsy, the SSE captured two latent traits associated with felt stigma. One trait represents feelings associated with epilepsy, which has been theorized as a substantial, yet previously unmeasured, part of felt stigma. The Brazilian SSE performs well across cultures, may be a more comprehensive measure for felt stigma, and may quantify stigmatizing attitudes among others.

## Introduction

Epilepsy-associated stigma is an often overlooked patient-centered outcome measure. Influenced by intrinsic patient factors, such as age of onset [189] and seizure severity [62], as well as external, societal forces [184], stigma has long been recognized as a substantial, yet potentially modifiable, force in the lives of people with epilepsy [55]. It has been repeatedly linked to decreased social well-being [357], poor health outcomes [364], and decreased patient satisfaction [62]. As a result, stigma-reduction efforts are ongoing [182,365]. However, there continues to be little consensus on how to best measure stigma.

From a theoretical perspective, epilepsy-associated stigma is frequently divided into two types: enacted stigma and felt stigma [55].

Enacted stigma describes beliefs held by people without epilepsy that, if acted upon, would lead to discrimination [54]. Enacted stigma is difficult to assess where discriminatory behaviors are socially undesirable. Most attempts to measure enacted stigma have involved surveys assessing the epilepsy-associated knowledge, attitudes and practices (KAP) of people without epilepsy to serve as a proxy for enacted stigma [366,367,55,368]. KAP surveys generally include culturally universal questions (e.g. "*would you let your child play with a child who has epilepsy*") which are sometimes complemented by questions specific to the population of the individuals assessed. KAP surveys often do not explicitly identify which items are assessing knowledge vs. attitudes vs. practices. When quantified at all, knowledge is usually totaled as a raw score. There are no agreed-upon scoring procedures for the attitude and practice items so this information is generally presented as response frequencies for individual items.

Felt stigma describes self-stigmatization by people with epilepsy that results from shame associated with epilepsy (internalized stigma) and fear of encountering enacted stigma

(anticipated stigma) [55,53,54]. International surveys identifying variations in epilepsy-associated stigma between countries suggest that stigma is a universal construct with distinct cultural elements [195,189,240]. Customized stigma assessment instruments may more completely capture the burden of stigma in its local context, but these are challenging to develop and validate and prohibit comparisons between cultures. The most frequently employed instrument for assessing felt stigma is Jacoby's 3-item Stigma Scale, adapted for use with people with epilepsy [236]. This instrument is used with other stigmatized conditions [369,174] and measures a person with epilepsy's perception of enacted stigma [179,69,229,370,185]. The original dichotomous responses for this popular instrument were revised to Likert-type scales to correct a noted ceiling effect [184,198], though the use of this version has been limited [371,212].

A cross-culturally relevant instrument which could quantify both felt stigma and stigmatizing KAPs would facilitate cross-cultural studies of stigma determinants and would be very valuable in outcome studies of stigma reduction interventions [61]. The Stigma Scale of Epilepsy (SSE) may fulfill this need. The SSE is a 24-item instrument that was designed to assess enacted stigma in the general public and felt stigma among people with epilepsy [233]. Each item is answered with four point Likert-type scales. A standardized stigma score is calculated (range 0-100) and is independent of the number of questions answered[p]. The SSE was developed and validated in Brazil [233] and has been used in India [200] and Bolivia [239].

[p] Formula for General Stigma Score

$$= \frac{[(\boldsymbol{sum\ of\ all\ answered\ items - number\ of\ answered\ items}) \times \mathbf{100}]}{[(\mathbf{4} \times \boldsymbol{number\ of\ answered\ questions}) - \boldsymbol{number\ of\ answered\ items}]}$$

We administered the SSE and Jacoby's 3-item Stigma Scale to Zambian people with epilepsy to assess the utility of the SSE in sub-Saharan Africa compared to the commonly employed Jacoby Stigma Scale. To determine the number of underlying traits assessed by both the SSE and Jacoby's 3-item Stigma Scale, we conducted an exploratory item factor analysis. We also conducted a confirmatory factor analysis of the SSE to examine the underlying traits assessed. Lastly, as previous research indicated that felt stigma varies based on individual characteristics, such as forced disclosure of epilepsy status [184,65], we assessed differential item functioning of the SSE.

## Methods

In October 2009, we interviewed 102 men, women, and youth (ages 12-18) with epilepsy at three different clinics in Zambia: two urban and one rural. The SSE and Jacoby's 3-item Stigma Scale were administered concurrently via interview. Basic demographic data, epilepsy characteristics, and disclosure status (among adults only) were also collected.

This study obtained ethical approval from the University of Zambia Biomedical Research Ethics Committee and the Michigan State University Biomedical Institutional Review Board.

### *Characteristics of the Study Sample*

Sixty-eight adults (44% female) and 34 youth (44% female) were interviewed. Demographic, clinical, and economic information for this population is shown in Table 2.1. Interviews were conducted in the context of a larger study with the following inclusion criteria: medical records confirming a diagnosis of epilepsy prior to study participation, and the ability to participate in group conversations in the local language (Nyanja, Bemba, or Tonga). Direct

**Table 2.1: Demographic and Clinical Information for People with Epilepsy Completing the Stigma Scale of Epilepsy**

| **Number (%)** | **Men (n=38)** | **Women (n=30)** | **Youth (n=34)** |
|---|---|---|---|
| Mean age, years (SD) | 32.2 (8.7) | 30.4 (9.7) | 15.2 (1.9) |
| Rural location, yes | 14 (36) | 12 (40) | 11 (32) |
| Marital status | | | |
| Never married | 19 (50) | 9 (30) | |
| Currently married (monogamous) | 13 (33) | 11 (37) | |
| Currently married (polygamous) | 3 (8) | 0 (0) | |
| Previously married[q] | 2 (5) | 8 (27) | |
| Remarried | 1 (3) | 2 (7) | |
| Educational status (adults: mean years in school; youth: currently in school, yes) | 8.2 (SD 3.7) | 6.1 (SD 3.3) | 27 (80) |
| Employment status, yes | 23 (59) | 5 (17) | - |
| Spouse employment status, yes (if applicable) | 3 (18) | 11 (85) | - |
| Median housing quality score (IQR) | 11.0 (6.0-12.0) | 12.0 (3.0-13.0) | 13.0 (6.0-13.0) |
| Median household wealth in Kwacha | K1,220,000 | K295,000 | K902,500 |
| Median in USD (IQR) | $358 (52-676) | $86 (9-256) | $264 (123-795) |
| Food Insecure, yes | 10 (26) | 10 (33) | - |
| Physical stigmata of epilepsy present[r] | 8 (21) | 14 (47) | - |
| Median age of epilepsy onset, years (IQR) | 16.5 (8-28) | 14.0 (11-20) | - |
| Most recent seizure | | | |
| ≤1 week ago | 10 (28) | 8 (27) | 9 (27) |
| >1 week ago to ≤1 month ago | 12 (33) | 5 (17) | 7 (21) |
| >1 month ago to ≤1 year ago | 8 (22) | 9 (31) | 7 (21) |
| >1 year ago | 6 (17) | 7 (24) | 11 (33) |
| Taking an antiepileptic drug (AED), yes | 37 (97) | 28 (93) | 32 (94) |
| Adherent to AED, yes | 20 (54) | 18 (64) | 21 (65) |
| Disclosure of epilepsy | | | |
| Yes, because I told them | 8 (20) | 5 (17) | - |
| Yes, because others told them or they saw me have a seizure | 19 (49) | 19 (63) | |
| No | 11 (28) | 6 (20) | |
| Shona Symptom Questionnaire, mean (SD) | 5.0 (3.1) | 5.6 (2.6) | 5.58 (3.4) |
| Requiring psychiatric support[s] | 18 (46) | 20 (67) | 15 (43) |

[q] Divorced, widowed, or separated and not remarried

[r] Primarily visible burn scars, interviewer assessed

[s] Scores > 5 using the Shona Symptom

**Table 2.1 (cont'd):**

| Number (%) | Men (n=38) | Women (n=30) | Youth (n=34) |
|---|---|---|---|
| Personal Safety | | | |
| Well, stream or river used as household water source[t] | 7 (18) | 5 (17) | 4 (12) |
| Kerosene/gas, candles or fire used for household lighting[u] | 22 (56) | 19 (63) | 15 (43) |
| Wood, charcoal or kerosene stove used for cooking[u] | 23 (59) | 20 (67) | 14 (40) |
| Familial physical abuse, yes | 6 (15) | 12 (40) | - |
| Rape, yes (women only) | - | 4 (13) | - |
| Transactional sex, yes (women only) | - | 3 (10) | - |

English to local language translations of the SSE and Jacoby's 3-item Stigma Scale were not performed as comprehensive local translations were not feasible. Zambia has seven official vernacular languages as well as immense variation in local dialects. Instead, as English is also an official language and the most common second language spoken by Zambians, both instruments were provided to interviewers in English. Interviewers participated in an afternoon training session on both the SSE and Jacoby's Stigma Scale so that the items could be translated from English to suit the dialect of each participant.

*Analytic Plan*

Interviews were originally conducted on paper and then entered into Microsoft Excel and verified for accuracy. Paper copies of the data were available for referral throughout analysis. Descriptive statistics were calculated for each item of the SSE and the distribution of item

[t] Proxy measure for increased risk of drowning

[u] Proxy measure for increased risk of burns

responses were compared to the original validation data from Sao Paulo, Brazil [233] using $\chi^2$ tests.

We used item response theory modeling (IRT) to examine the validity of the SSE for our study sample [372]. This approach stipulates that an individual with epilepsy's responses to the SSE's items are a combination of the levels of an individuals' underlying latent traits and characteristics of the SSE items. In this case, the underlying latent traits assessed by the SSE pertain to epilepsy-associated stigma. The number of underlying latent traits assessed by a series of questions can be determined by assessing item dimensionality with a Scree plot. A Scree plot depicts the number of possible factors for an instrument on the x-axis and the amount of variation in item responses that is attributed to each factor (the factor's eigenvalue) on the y-axis [372]. The number of latent traits assessed by an instrument occurs where the eigenvalues begin to level off on the Scree plot (i.e. the "elbow" of the graph) [373]. For these analyses, SSE item-related characteristics were modeled in terms of difficulty and discrimination [372]. Item difficulty indicates the degree to which an item is difficult to endorse; individuals with lower levels of epilepsy-associated stigma are less likely to endorse an item with higher difficulty. For Likert-type items, difficulties are calculated for each transition between adjacent response categories. Item discriminations quantify the extent to which response categories for each item distinguish individuals with different levels of epilepsy-associated stigma. Similar to factor loadings, item discriminations also reflect how strongly an item is related to the underlying latent traits. We used IRT in both exploratory and confirmatory approaches to examine the dimensionality of the SSE items to better understand the nature of stigma as measured by the SSE and Jacoby's 3-item Stigma Scale [374].

A fundamental assumption of IRT is that variations in responses to items are directly determined by variations in the underlying latent traits assessed and not by unrelated extrinsic factors [372,375]. Differential item functioning analysis considers this assumption by investigating the similarity between the item responses of individuals with similar levels of the underlying latent traits but different levels of some extrinsic characteristic. Previous research among individuals with highly stigmatized conditions such as epilepsy and HIV suggest that those who have their condition involuntarily disclosed to their community experience greater felt stigma [184,98,65,137]. We used differential item functioning analysis to examine the effect of forced disclosure of epilepsy on individual responses to the SSE.

Descriptive statistics and comparisons to data gathered in Brazil [233] were performed using SAS (version 9.3, SAS, Cary). Mplus (version 7.11, Muthén & Muthén, Los Angeles) was used to conduct exploratory and confirmatory IRT analyses with the SSE. Analyses of underlying latent traits and differential item functioning were completed using IRTPRO (version 2.1, Scientific Software International, Inc, Lincolnwood).

## Results

### *Descriptive Statistics*

Participants exhibited a full range of felt stigma using the SSE and Jacoby's 3-item Stigma Scale as shown in Table 2.2. According to the Jacoby's 3-item Stigma Scale, 41 adults (60%) and 27 youth (79%) experienced some level of felt stigma. Each participant provided responses to all SSE items, with the exception of six individuals (6%, all of whom were youth) who declined to answer the question regarding marriage. Generally, IRT ignores missing data as it has no effect on latent trait level estimates.

**Table 2.2: Felt stigma measures using the SSE and Jacoby's 3-item Stigma Scale**

| **Stigma Scale of Epilepsy, Number (%)** | | | | | |
|---|---|---|---|---|---|
| | **Not at all** | **A Little** | **A Lot** | **Totally** | **Missing** |
| Question 1: Do you think that people with epilepsy feel able to control their own epilepsy? | | | | | |
| 1. Control | 39 (38.2) | 21 (20.6) | 24 (23.5) | 18 (17.7) | 0 (0) |
| Question 2: How would you feel when you see an epileptic seizure? | | | | | |
| 2. Scared | 54 (52.9) | 14 (13.7) | 16 (15.7) | 16 (15.7) | 2 (1.9) |
| 3. Fear | 55 (53.9) | 15 (14.7) | 19 (18.6) | 11 (10.7) | 2 (1.9) |
| 4. Sadness | 26 (25.4) | 10 (9.8) | 22 (21.6) | 42 (41.2) | 2 (1.9) |
| 5. Pity | 4 (3.9) | 7 (6.8) | 43 (42.2) | 46 (45.1) | 2 (1.9) |
| Question 3: Which difficulties do you think people with epilepsy have in their daily lives? | | | | | |
| 6. Relationships | 28 (27.4) | 24 (23.5) | 32 (31.4) | 16 (15.7) | 2 (1.9) |
| 7. Work | 14 (13.7) | 21 (20.6) | 42 (41.2) | 21 (20.6) | 4 (3.9) |
| 8. School | 19 (19) | 18 (18) | 32 (32) | 32 (32) | 1 (1) |
| 9. Friendships | 23 (23) | 29 (28) | 35 (34) | 15 (15) | 0 (0) |
| 10. Sexual | 34 (34) | 18 (18) | 27 (27) | 20 (20) | 1 (1) |
| 11. Emotional | 28 (28) | 18 (18) | 31 (30) | 25 (25) | 0 (0) |
| 12. Prejudice | 18 (18) | 19 (19) | 39 (38) | 26 (25) | 0 (0) |
| Question 4: How do you think that people with epilepsy feel? | | | | | |
| 13. Worried | 7 (7) | 10 (10) | 43 (42) | 42 (41) | 0 (0) |
| 14. Dependent | 38 (37) | 16 (16) | 30 (29) | 18 (18) | 0 (0) |
| 15. Incapable | 38 (37) | 28 (28) | 21 (21) | 15 (15) | 0 (0) |
| 16. Fearful | 26 (26) | 14 (14) | 34 (33) | 28 (28) | 0 (0) |
| 17. Depressed | 24 (24) | 25 (25) | 34 (33) | 19 (19) | 0 (0) |
| 18. Ashamed | 32 (31) | 13 (13) | 28 (28) | 29 (28) | 0 (0) |
| 19. The same as those without epilepsy | 68 (67) | 10 (10) | 6 (6) | 18 (18) | 0 (0) |
| Question 5: In your opinion, the prejudice in epilepsy will be related to? | | | | | |
| 20. Relationships | 29 (29) | 22 (22) | 33 (33) | 16 (16) | 1 (1) |
| 21. Marriage | 29 (30) | 22 (23) | 30 (31) | 15 (16) | 6 (6) |
| 22. Work | 15 (15) | 19 (19) | 36 (37) | 28 (29) | 3 (3) |
| 23. School | 20 (20) | 16 (16) | 33 (33) | 33 (33) | 0 (0) |
| 24. Family | 41 (40) | 25 (25) | 23 (23) | 13 (13) | 0 (0) |
| **Jacoby's 3-item Stigma Scale, n (%)** | | | | | |
| "Because of my epilepsy…"<br>I feel some people are uncomfortable with me, yes<br>I feel some people treat me like an inferior person, yes<br>I feel some people would prefer to avoid me, yes | | | | | 54 (53)<br>48 (47)<br>45 (44) |

Table 2.3 compares the frequency of responses from Zambian people with epilepsy to the responses given by original Brazilian validation population. Generally, Zambian people with epilepsy selected responses indicating greater stigma than Brazilian people with epilepsy. Despite this, significantly more Zambian individuals with epilepsy believe that people with epilepsy can control their epilepsy ($p<0.001$). In addition, people with epilepsy in Brazil expressed feeling more scared ($p<0.0001$) and fear ($p=0.003$) than people with epilepsy in Zambia, as well as feeling more dependent ($p=0.02$). There were no significant differences in reported depression, difficulties at work or with friendships and sexual relationships.

**Table 2.3: Comparison of SSE responses from Zambia (n=102) and Brazil (n=40)**

| **Number (%)** | **Country**[v] | **Not at all** | **A Little** | **A Lot** | **Totally** | **Miss-ing** | **p-value** |
|---|---|---|---|---|---|---|---|
| Question 1: Do you think that people with epilepsy feel able to control their own epilepsy? | | | | | | | |
| Control | Zambia | 39 (38.2) | 21 (20.6) | 24 (23.5) | 18 (17.7) | 0 (0) | **<0.001** |
| | Brazil | 17 (42.5) | 11 (27.5) | 10 (25.0) | 2 (5.0) | 0 (0) | |
| Question 2: How would you feel when you see an epileptic seizure? | | | | | | | |
| Scared | Zambia | 54 (52.9) | 14 (13.7) | 16 (15.7) | 16 (15.7) | 2 (1.9) | **<0.001** |
| | Brazil | 13 (32.5) | 9 (22.5) | 12 (30.0) | 6 (15.0) | 0 (0) | |
| Question 3: How would you feel when you see an epileptic seizure? | | | | | | | |
| Fear | Zambia | 55 (53.9) | 15 (14.7) | 19 (18.6) | 11 (10.7) | 2 (1.9) | **0.003** |
| | Brazil[w] | 23 (57.5) | 5 (12.5) | 10 (25.0) | 9 (22.5) | 0 (0) | |
| Sadness | Zambia | 26 (25.4) | 10 (9.8) | 22 (21.6) | 42 (41.2) | 2 (1.9) | **<0.001** |
| | Brazil | 7 (17.5) | 10 (25.0) | 15 (37.5) | 8 (20.0) | 0 (0) | |
| Pity | Zambia | 4 (3.9) | 7 (6.8) | 43 (42.2) | 46 (45.1) | 2 (1.9) | **<0.001** |
| | Brazil | 9 (22.5) | 12 (30.0) | 10 (25.0) | 9 (22.5) | 0 (0) | |
| Question 4: Which difficulties do you think people with epilepsy have in their daily lives? | | | | | | | |
| Relationships | Zambia | 28 (27.4) | 24 (23.5) | 32 (31.4) | 16 (15.7) | 2 (1.9) | **<0.001** |
| | Brazil | 15 (37.5) | 10 (25.0) | 13 (32.5) | 2 (5.0) | 0 (0) | |
| Work | Zambia | 14 (13.7) | 21 (20.6) | 42 (41.2) | 21 (20.6) | 4 (3.9) | 0.764 |
| | Brazil | 6 (15.0) | 9 (22.5) | 15 (37.5) | 10 (25.0) | 0 (0) | |

[v] Data for Brazil drawn directly from Fernandes et al. [233]

[w] As printed in Fernandes et al. [233]

**Table 2.3 (cont'd)**

| Number(%) | Country[x] | Not at all | A Little | A Lot | Totally | Miss-ing | p-value |
|---|---|---|---|---|---|---|---|
| School | Zambia | 19 (18.6) | 18 (17.6) | 32 (31.4) | 32 (31.4) | 1 (0.9) | **<0.001** |
| | Brazil | 7 (17.5) | 13 (32.5) | 15 (37.5) | 5 (12.5) | 0 (0) | |
| Friendships | Zambia | 23 (22.6) | 29 (28.4) | 35 (34.3) | 15 (14.7) | 0 (0) | 0.203 |
| | Brazil[y] | 13 (32.5) | 11 (27.5) | 11 (27.5) | 6 (12.5) | 0 (0) | |
| Sexual | Zambia | 34 (33.3) | 18 (17.6) | 27 (26.4) | 20 (19.6) | 3 (2.9) | 0.086 |
| | Brazil | 17 (42.5) | 6 (15.0) | 12 (30.0) | 5 (12.5) | 0 (0) | |
| Emotional | Zambia | 28 (27.5) | 18 (17.7) | 31 (30.4) | 25 (24.5) | 0 (0) | **<0.001** |
| | Brazil | 6 (10.0) | 10 (25.0) | 18 (45.0) | 6 (15.0) | 0 (0) | |
| Prejudice | Zambia | 18 (17.7) | 19 (18.6) | 39 (38.2) | 26 (25.5) | 0 (0) | **<0.001** |
| | Brazil | 12 (30.0) | 12 (30.0) | 4 (10.0) | 12 (30%) | 0 (0) | |
| Question 4: How do you think that people with epilepsy feel? | | | | | | | |
| Worried | Zambia | 7 (6.9) | 10 (9.8) | 43 (42.2) | 42 (41.2) | 0 (0) | **0.009** |
| | Brazil | 7 (17.5) | 6 (15.0) | 14 (35.0) | 13 (32.5) | 0 (0) | |
| Dependent | Zambia | 38 (37.3) | 16 (15.7) | 30 (29.4) | 18 (17.7) | 0 (0) | **0.02** |
| | Brazil | 11 (27.5) | 8 (20.0) | 10 (25.0) | 11 (27.5) | 0 (0) | |
| Incapable | Zambia | 38 (37.3) | 28 (27.4) | 21 (20.6) | 15 (14.7) | 0 (0) | **<0.001** |
| | Brazil | 23 (57.5) | 8 (20.0) | 3 (7.5) | 6 (15.0) | 0 (0) | |
| Fearful | Zambia | 26 (25.5) | 14 (13.7) | 34 (33.3) | 28 (27.5) | 0 (0) | **<0.001** |
| | Brazil | 12 (30.0) | 11 (27.5) | 13 (32.5) | 4 (10.0) | 0 (0) | |
| Depressed | Zambia | 24 (23.5) | 25 (24.5) | 34 (33.3) | 19 (18.6) | 0 (0) | 0.28 |
| | Brazil | 10 (25.0) | 10 (25.0) | 9 (22.5) | 10 (25.0) | 1 (5.0) | |
| Ashamed | Zambia | 32 (31.4) | 13 (12.8) | 28 (27.5) | 29 (28.4) | 0 (0) | **0.008** |
| | Brazil | 15 (37.5) | 9 (22.5) | 9 (22.5) | 7 (17.5) | 0 (0) | |
| The same as those without epilepsy | Zambia | 68 (66.7) | 10 (9.8) | 6 (5.9) | 18 (17.7) | 0 (0) | **<0.001** |
| | Brazil | 20 (50.0) | 7 (17.5) | 9 (22.5) | 3 (7.5) | 1 (5.0) | |
| Question 5: In your opinion, the prejudice in epilepsy will be related to? | | | | | | | |
| Relationships | Zambia | 29 (28.4) | 22 (21.6) | 33 (32.4) | 16 (15.7) | 2 (1.9) | **<0.001** |
| | Brazil | 8 (20.0) | 15 (37.5) | 14 (35.0) | 3 (7.5) | 0 (0) | |
| Marriage | Zambia | 29 (28.4) | 22 (21.6) | 30 (29.4) | 15 (14.7) | 6 (5.9) | 0.23 |
| | Brazil | 15 (27.5) | 9 (22.5) | 12 (30.0) | 4 (10.0) | 0 (0) | |
| Work | Zambia | 15 (14.7) | 19 (18.6) | 36 (35.3) | 28 (27.5) | 4 (3.9) | 0.1 |
| | Brazil | 9 (22.5) | 9 (22.5) | 14 (35.0) | 8 (20.0) | 0 (0) | |
| School | Zambia | 20 (19.6) | 16 (15.7) | 33 (32.4) | 33 (32.4) | 0 (0) | **0.002** |
| | Brazil | 10 (25.0) | 7 (17.5) | 16 (40.0) | 7 (17.5) | 0 (0) | |
| Family | Zambia | 41 (40.2) | 25 (24.5) | 23 (22.6) | 13 (12.8) | 0 (0) | **0.01** |
| | Brazil | 16 (40.0) | 15 (37.5) | 6 (15.0) | 3 (7.5) | 0 (0) | |

[x] Data for Brazil drawn from drawn from Fernandes et al.

[y] As printed in Fernandes et al. [233]

*SSE Dimensionality*

To examine the number of latent traits assessed by the SSE, Mplus (version 7.11, Muthén & Muthén, Los Angeles was used for exploratory item factor analysis. The exploratory factor analysis supported a model with two factors that represented two underlying latent traits (eigenvalues 7.956 and 3.200, respectively). This can be seen in the associated scree plot in Figure 2.1. The two factor model accounted for 46.5% of the cumulative variance seen in item responses, as shown in Figure 2.2. An item was considered to contribute to a latent factor if its promax-rotated loading for that factor was greater than 0.4. Item 1 ("*Do you think that people with epilepsy feel able to control their own epilepsy*?") did not load onto either factor and was eliminated from further analysis. The first factor included questions regarding the difficulties faced and prejudice associated with epilepsy, whereas the second factor included questions regarding the respondent's sentiments when he/she witnesses a seizure and how the respondent believes that people with epilepsy feel.

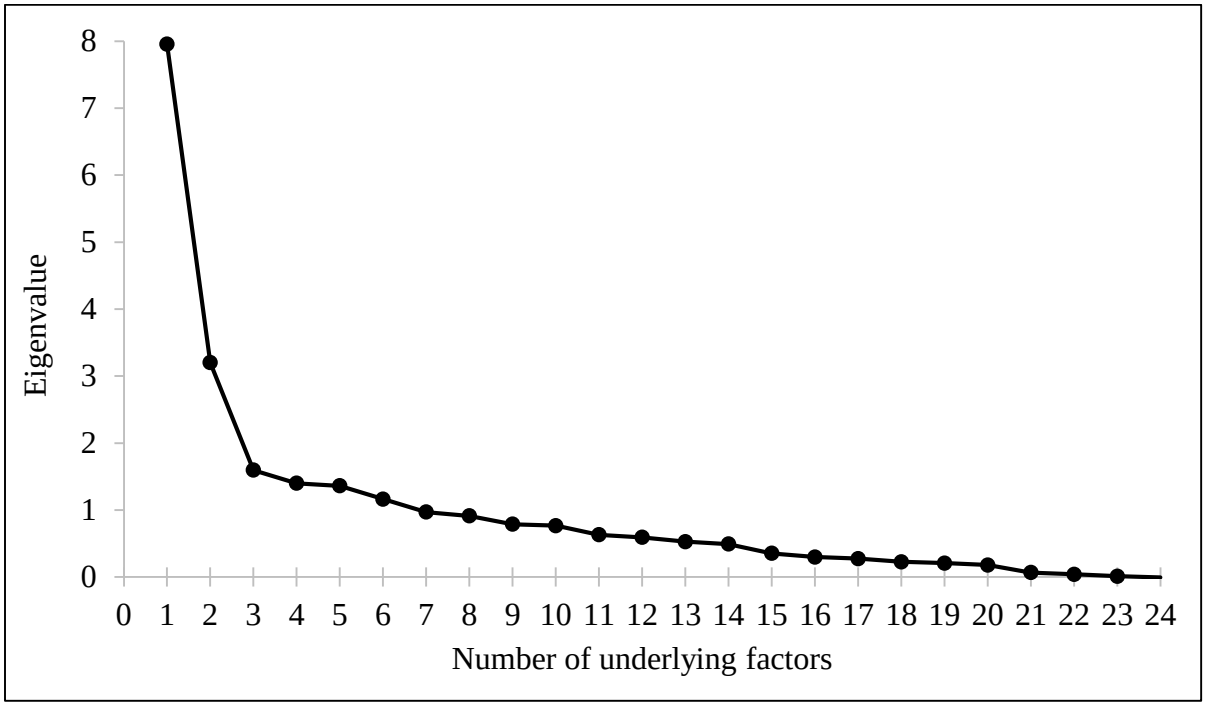


**Figure 2.1: Scree plot for Stigma Scale of Epilepsy Exploratory Factor Analysis**

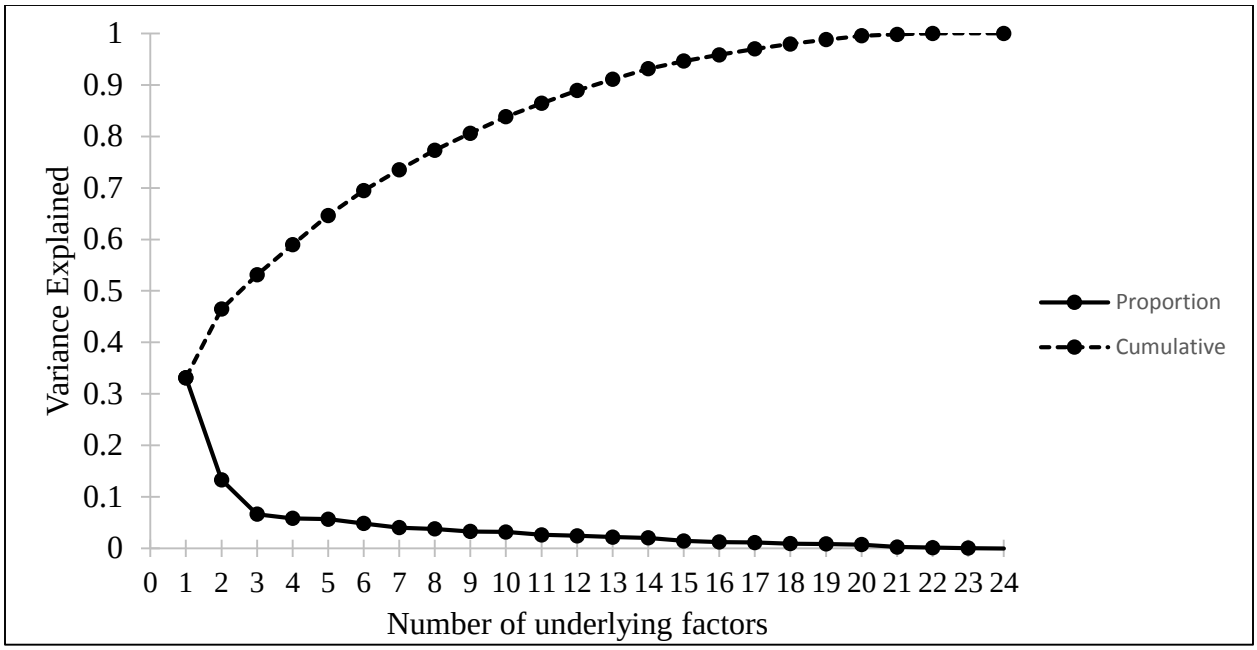


**Figure 2.2: Proportion and Cumulative Proportion of Variance Explained by Each Factor**

The two latent factors were moderately correlated (-0.41) with a high correlation between items 2 and 3 ("*How would you feel when you see an epileptic seizure?" 2: Scared and 3: Fear*) (0.979). Further inquiry attributed this, in part, to translation. In two of the local languages (Nyanja and Bemba), scared and fear are often described using nearly identical words. Because fear had a higher factor loading than scared, scared was removed from further analysis.

Discriminations for each item are reported in Table 2.4. The discrimination for item 3 ("*How do you feel when you see an epileptic seizure*?" *3: Fear*) was large (37.14) indicating that as an individual's stigma level increases, responses to this item also increased, allowing discrimination between individuals with low and high levels of stigma.

To compare the two underlying latent traits assessed by the SSE to those assessed by Jacoby's 3-item Stigma Scale, a second confirmatory analysis was run in which the items from Jacoby's 3-item Stigma Scale were loaded along with the SSE items onto both of the factors

**Table 2.4: Item Discrimination and Difficulties[z]**

| | Discriminations | | Difficulties | | |
|---|---|---|---|---|---|
| | **Latent factor 1 (se)** | **Latent factor 2 (se)** | **Not at all to A little (se)** | **A little to A lot (se)** | **A lot to Totally (se)** |
| *Question 1: Do you think that people with epilepsy feel able to control their own epilepsy?* | | | | | |
| 1. Control | Not included in model | | | | |
| *Question 2: How would you feel when you see an epileptic seizure?* | | | | | |
| 2. Scared | Not included in model | | | | |
| 3. Fear | - | 1.57 (0.36) | -0.35 (0.26) | -1.26 (0.29) | -2.79 (0.41) |
| 4. Sadness | - | 1.86 (0.4) | 1.6 (0.34) | 0.85 (0.29) | -0.55 (0.27) |
| 5. Pity | - | 1.13 (0.29) | 3.7 (0.56) | 2.56 (0.39) | -0.19 (0.23) |
| *Question 3: Which difficulties do you think people with epilepsy have in their daily lives?* | | | | | |
| 6. Relationships | - | 1.45 (0.31) | 1.28 (0.29) | -0.17 (0.24) | -2.25(0.35) |
| 7. Work | 0.71 (0.23) | - | 1.99 (0.31) | 0.69 (0.23) | -1.4 (0.26) |
| 8. School | 1.37 (0.31) | - | 1.9 (033) | 0.71 (0.25) | -1.02 (0.26) |
| 9. Friendships | 1.33 (0.29) | - | 1.55 (0.29) | -0.1 (0.23) | -2.24 (0.34) |
| 10. Sexual | 1.84 (0.4) | - | 0.91 (0.29) | -0.23 (0.27) | -2.1 (0.39) |
| 11. Emotional | 1.48 (0.32) | - | 1.3 (0.28) | 0.21 (0.24) | -1.56 (0.29) |
| 12. Prejudice | 1.28 (0.29) | - | 1.97 (0.31) | 0.7 (0.24) | -1.4 (0.28) |
| *Question 4: How do you think that people with epilepsy feel?* | | | | | |
| 13. Worried | - | 1.34 (0.29) | 3.28 (0.47) | 2.13 (0.35) | -0.46 (0.24) |
| 14. Dependent | - | 2.03 (0.42) | 0.82 (0.3) | -0.32 (0.28) | -2.52 (0.42) |
| 15. Incapable | - | 1.78 (0.38) | 0.74 (0.27) | -1.02 (0.30) | -2.57 (0.41) |
| 16. Fearful | - | 1.43 (0.31) | 1.4 (0.28) | 0.51 (0.24) | -1.36 (0.29) |
| 17. Depressed | 1.08 (0.27) | - | 0.94 (0.24) | 0.25 (0.22) | -1.14 (0.33) |
| 18. Ashamed | - | 1.4 (0.3) | 1.52 (0.28) | 0.05 (0.24) | -1.98 (0.25) |
| 19. The same as those without epilepsy | - | 0.31 (0.24) | 1.56 (0.26) | 1.19 (0.23) | 0.7 (0.21) |
| *Question 5: In your opinion, the prejudice in epilepsy will be related to?* | | | | | |
| 20. Relationships | 1.67 (0.36) | - | 1.22 (0.29) | -0.16 (0.26) | -2.39 (0.4) |
| 21. Marriage | 1.59 (0.35) | - | 1.26 (0.3) | -0.14 (0.26) | -2.33 (0.38) |
| 22. Work | 1.01 (0.26) | - | 2.01 (0.32) | 0.77 (0.24) | -1.08 (0.25) |
| 23. School | 1.16 (0.28) | - | 1.71 (0.29) | 0.74 (0.24) | -0.89 (0.24) |
| 24. Family | - | 1.18 (0.29) | 0.43 (0.23) | -0.82 (0.24) | -2.36 (0.35) |

[z]Item discriminations and difficulties obtained as part of a confirmatory factor analysis conducted in IRTPRO (version 2.1, Scientific Software International, Inc, Lincolnwood).

identified during the exploratory factor analysis. This second confirmatory analysis demonstrated significant factor loadings for Jacoby's 3-item Stigma Scale only on the first latent factor; the items did not load onto the second factor with promax-rotated loadings greater than 0.4. This indicates that Jacoby's 3-item Stigma Scale assesses only one latent trait associated with felt stigma, whereas the SSE assesses two.

*Differential Item Functioning*

Among adults, the effect of epilepsy disclosure status on responses to the SSE was tested using an exploratory invariance analysis in IRTPRO (version 2.1, Scientific Software International, Inc, Lincolnwood). Of the 68 adult participants, 38 (56%) reported forced disclosure of their epilepsy status. An exploratory invariance analysis examines differential item functioning by conditioning responses to individual items and levels of underlying latent factors on the potential source of bias, in this case forced disclosure. SSE item discriminations were held constant and two difficulty estimates for each item's 4-point Likert-type response categories were estimated, one for respondents that have experienced forced disclosure and one for respondents that have not. A significant difference in difficulty estimates between these groups indicates that differential item functioning based on forced disclosure of epilepsy exists.

As shown in Table 2.5, differential item functioning was present for items 5 and 13. The difficulty estimates suggest that people with epilepsy who experience forced disclosure endorse feeling more pity (item 5) when they see an epileptic seizure than those who have not experienced forced disclosure. It also suggests that people with epilepsy who experience forced disclosure also attribute greater worry (item 13) to people with epilepsy than those without

forced disclosure. Both of these items are associated with the second factor, suggesting that that forced disclosure may heighten the negative feelings associated with an epilepsy diagnosis.

**Table 2.5: Differential Item Functioning of Stigma Scale of Epilepsy Items**

| **Difficulties (standard error):**[aa] | | **Not at all to A little** | **A little to A lot** | **A lot to Totally** | **p-value** |
|---|---|---|---|---|---|
| *Question 2: How would you feel when you see an epileptic seizure?* | | | | | |
| 5. Pity | Forced disclosure | -2.15 (0.58) | 0.27 (0.28) | - | **0.001** |
| | No forced disclosure | -2.0 (0.57) | -1.44 (0.44) | -0.22 (0.32) | |
| *Question 4: How do you think that people with epilepsy feel?* | | | | | |
| 13. Worried | Forced disclosure | -2.05 (0.55) | -1.16 (0.36) | 0.55 (0.29) | **0.046** |
| | No forced disclosure | -2.58 (0.70) | -0.08 (0.32) | - | |

**Discussion**

Despite substantial literature examining epilepsy-associated stigma and its impact on people with epilepsy, considerable gaps remain in our understanding of this formidable patient-centered outcome. The distinction between felt and enacted stigma has long been recognized, as has the belief that felt stigma can be present even in the absence of enacted stigma [53,54]. Social scientists suggest that this contradiction is because felt stigma is influenced by both an individual with epilepsy's interpretation of enacted stigma as well as individual sentiments associated with a diagnosis of epilepsy [69]. Yet, commonly-employed instruments appear not to capture the latter aspect of felt stigma. Our findings further support concerns that Jacoby's 3-item Stigma Scale does not capture an individual with epilepsy's sentiments associated with an epilepsy diagnosis, which are believed to be an essential component of felt stigma [54].

[aa] Item discriminations and difficulties obtained as part of a confirmatory factor analysis conducted in IRTPRO (version 2.1, Scientific Software International, Inc, Lincolnwood).

Researchers using Jacoby 3-item Stigma Scale for other stigmatized conditions may need to consider developing additional stigma instruments.

The analysis presented here suggests that the SSE can identify both an individual with epilepsy's perception of difficulties and prejudices associated with epilepsy (anticipated stigma) as well as the individual's sentiments associated with epilepsy and witnessing a seizure (internalized stigma), whereas the popular Jacoby 3-item Stigma Scale only identifies the former aspect of felt stigma. Although the SSE has been critiqued for including questions regarding epilepsy's impact on people with epilepsy [55], these questions, which load onto the second latent trait, appear to represent an individual's sentiments, including shame, regarding epilepsy. If these findings are confirmed using other populations of people with epilepsy, the SSE may provide substantial insight into felt stigma.

This analysis also offers suggestions for improving the SSE. The removal of item 1 because it did not load onto either latent trait as well as a significant correlation between items 2 and 3 (scared and fear) suggests that the SSE could be shortened. Subsequent investigations using the SSE have attempted to address inter-item correlation; in Bolivia, Bruno et al. replaced "scared" with "shock", although it is unclear what effect this has had on the SSE's underlying latent traits [239]. In addition, because the SSE assesses two distinct aspects of felt stigma, a summary stigma score should be designed to represent both elements. Unfortunately, the standardized stigma score calculation provided by Fernandes et al. [233] may obscure these latent traits. For this reason, we recommend the use of IRT analysis for the design of a new standardized stigma score for the SSE.

To the best of our knowledge, this is the largest sample of people with epilepsy to complete the SSE to date. As part of this study, we compared the responses of people with

epilepsy in Zambia to the responses of people with epilepsy in Brazil and found that our urban and rural population of Zambians generally expressed greater underlying stigma than an urban population of Brazilians. Although this instrument has also been used in India and Bolivia, comparisons were not made to these published data because individuals' responses to individual SSE items were either combined with responses from the general public [239], or only standardized stigma scores were provided [200].

Some limitations of this work deserve mention. As all of the people with epilepsy surveyed were identified through the clinic where they receive epilepsy care, survey respondents are not representative of the general population of people with epilepsy in this setting due to Zambia's sizable epilepsy treatment gap. In addition, as this data collection was part of a larger study, the stigma measures were administered only to people with epilepsy and reliability of the SSE was not examined. Future research should examine the measurement properties of the SSE when it is administered to individuals without epilepsy.

Since initiating this study, two additional felt stigma measures have been published. The Kilifi Stigma Scale was developed as a culturally appropriate measure for felt stigma experienced by people with epilepsy in Kenya, however, the authors' factor analysis indicated that, like the 3-item stigma scale, only one underlying latent trait is assessed by the instrument [240]. The construct validity of the Kilifi Stigma Scale in relation to other measures also remains unknown as well as its applicability outside of Kenya. In addition, the Stigma Scale for Chronic Illness was developed to assess stigma experienced by individuals with neurological conditions in the United States, however, transnational data using this scale has yet to be published [249].

Social stigma continues to be a significant problem for people with epilepsy in developed and developing countries and accurate characterization of it is essential for stigma reduction interventions to succeed. The SSE appears to capture aspects of felt stigma that were previously theorized yet never quantified. This instrument may improve our understanding of epilepsy-associated stigma, especially if it is found to accurately assess enacted stigma.

# CHAPTER 3:

# LAYERED HIV-RELATED AND EPILEPSY-ASSOCIATED STIGMA IN ZAMBIA


## Abstract

*Objective*

Disease-associated stigma hinders care delivery for conditions such as HIV and epilepsy. Layered stigma, which describes stigma experienced by individuals with multiple stigmatized conditions, is often overlooked in stigma research. Layered stigma resulting from comorbid medical conditions is poorly characterized, may have a multiplicative rather than an additive effect, and may hinder the success of stigma interventions.

*Methods*

To better understand layered stigma, we assessed HIV-related and epilepsy-associated stigma among people with HIV & epilepsy, people with HIV only, and people with epilepsy only in Zambia. Questions assessed demographic and clinical characteristics; epilepsy-associated stigma; HIV-related stigma; and psychiatric morbidity. Stigma instruments were disease specific. Jacoby's 3-item Stigma Scale and Stigma Scale of Epilepsy were used to assess epilepsy-associated stigma whereas Jacoby's 3-item Stigma Scale and HIV/AIDS Stigma Instrument-PLWA were used for HIV-related stigma. The Shona Symptom Questionnaire was used to assess psychiatric morbidity.

Demographic and clinical characteristics were compared between groups using t-tests or $\chi^2$ tests, as appropriate. Contingency tables were used to compare epilepsy-associated and HIV-related

stigma reported by people with HIV & epilepsy to that reported people with HIV only and people with epilepsy only. Summary scores for Jacoby's Stigma Scale, the Stigma Scale of Epilepsy, the HIV/AIDS Stigma Instrument-PLWA and Shona Symptom Questionnaire were compared across groups using t-tests.

*Results*

We interviewed 101 people – 20 with HIV & epilepsy, 40 with HIV only, and 41 with epilepsy only. There were significant demographic and clinical differences between the three groups. People with HIV only were more likely to be older, female and employed than people with HIV & epilepsy and people with epilepsy only ($p<0.0001$ for all). People with epilepsy only were more likely to report familial abuse than people with HIV only and people with HIV & epilepsy ($p=0.0051$). People with epilepsy only were diagnosed with epilepsy at a younger age than people with HIV & epilepsy ($p=0.0369$), whereas people with HIV & epilepsy were younger when diagnosed with HIV than people with HIV only ($p=0.0327$). People with HIV & epilepsy were also more likely to have a seizure in the past month than people with epilepsy only ($p=0.0399$).

No significant differences in epilepsy-associated stigma were reported by people with HIV & epilepsy and people with epilepsy only. However, there were differences in HIV-related stigma between people with HIV & epilepsy and people with HIV only. People with HIV & epilepsy were more likely to feel like others blamed them for their HIV status (OR: 5.29 [1.16-24.07]) and like they were no longer a person (OR: 5.29 [1.16-24.07]) than people with HIV only. No significant differences in psychiatric morbidity were found between the three groups.

*Conclusion*

Comorbid HIV and epilepsy is associated with increased HIV-related stigma. No significant differences in epilepsy-associated stigma were detected, though this may be because a majority of individuals in the HIV & epilepsy group (75%) were diagnosed with epilepsy before they were diagnosed with HIV. Layered stigma is apparent among individuals with HIV & epilepsy. Future research should examine the impact of order of diagnoses on layered stigma as well as layered stigma's impact on health outcomes.

## Introduction

Forty years after Goffman's original treatise [44], stigma has come to be considered a "fundamental cause of population health inequity" [68]. Stigmatization is a discrediting sociocultural process that involves stereotyping and discrimination directed at individuals with traits that are viewed negatively by society [44,45]. For conditions like HIV and epilepsy, disease-associated stigma is one of the greatest barriers to improving the availability of care and preventing mortality [25,7,30,376,51]. HIV-related stigma is also associated with decreased voluntary HIV testing [127,128,110,129-131] as well as decreased health care seeking behaviors [91,142,131,143]. As a result, substantial resources have been invested to examine predictors of disease-associated stigma. Age at disease onset [203,193,197]; disease severity [95,96,54,377,202] and duration[377,194]; low socioeconomic status [95,378,185]; and female gender [75,113,118,192] have been associated with increased reported stigma. Meanwhile, increased levels of education [197,111,112,196] and social support [100,114,62] have been associated with decreased stigma. The widespread effects of disease-associated stigma are also well documented. Increased stigma has been associated with decreased voluntary disclosure of disease [127,129]; increased psychiatric morbidity [153,95,196,213,225]; decreased quality of life [152,198,200]; and decreased medication adherence [97,379,195,148].

Previous studies examining disease-associated stigma and its impact were primarily condition-specific or comparisons between stigmatized conditions [68,46,52,380]. Although individual demographic and clinical characteristics have been shown to affect stigma experiences, considerably less research has focused on individuals that are affected by more than one stigmatized condition [107,242]. This layered [81,381] or double [244] stigma has received little attention thus far, possibly because there are no validated quantitative instruments to assess

layered stigma from the perspective of stigmatized individuals [81]. However, neglecting layered stigma has likely led to an underestimation of the impact of disease-associated stigma [46], especially among individuals with more than one highly stigmatized condition.

Most studies examining layered stigma have focused on variations in stigma based on individual characteristics or behaviors, such as race, gender, homosexuality or injection drug use [242,244]. Research addressing layered stigma due to comorbid medical conditions has largely studied infectious diseases that are clinically related [246,247,245]. Qualitative and quantitative findings suggest that comorbid infectious diseases increase the stigma experienced by an individual [246,245], however, limited data exists regarding layered stigma from two non-communicable diseases or from an infectious and a non-communicable disease. As the burden of non-communicable diseases continues to grow in low- and low-middle income countries [382-384], understanding layered stigma experienced individuals with comorbid infectious and non-communicable diseases will become increasingly relevant. Walkup et al. investigated layered stigma from HIV and schizophrenia, but this was done by assessing attitudes among the general public towards individuals with HIV and schizophrenia and not by interviewing affected individuals [247]. As individuals can report feeling stigmatized even without encountering overt discrimination [54], layered stigma must also be assessed from the perspective of the affected individual. It is also important to examine the impact of layered stigma on health outcomes commonly associated with stigmatized conditions. Individuals with HIV and another chronic condition reported worse mental health outcomes than the general Tanzanian population [385], but it is unclear if stigma played a role in decreasing mental health.

HIV/AIDS remains one of the most common infectious diseases worldwide [5,1] and predisposes individuals to several non-communicable diseases, including epilepsy [386,387].

The development of new-onset seizures has been reported in 11% of HIV-positive individuals [15-17]. In addition, as HIV and epilepsy are both prevalent in resource-limited settings like sub-Saharan Africa [13,1], people with pre-existing epilepsy may also acquire HIV infection. Despite the substantial overlap between HIV and epilepsy, little is known about the demographic or clinical characteristics of patients with both HIV and epilepsy. Since HIV and epilepsy are both highly stigmatized [388,71,7], individuals with comorbid HIV and epilepsy may experience substantial layered stigma.

To better characterize the patient population with comorbid HIV and epilepsy and to examine the impact of layered stigma on reported disease-associated stigma, we interviewed individuals with comorbid HIV and epilepsy, individuals with HIV only, and individuals with epilepsy only. Standard stigma instruments were used to assess HIV-related and epilepsy-associated stigma. Demographic and clinical characteristics were collected. Psychiatric morbidity, an outcome commonly associated with disease-associated stigma, was also examined.

**Methods**

Interviews were conducted with patients obtaining routine outpatient care for HIV or epilepsy at two urban health care centers in Zambia. Five clinics were sampled for eligible participants: adult infectious disease, neurology, general medicine, psychiatry and epilepsy. At the adult infectious disease and epilepsy clinics, patients whose file numbers ended in 0, 4, 5, and 9 were assessed for study inclusion. A convenience sample was drawn from the other clinics due to a smaller eligible patient population. Eligibility criteria included: age 18-60 years; documentation of a diagnosis of HIV, epilepsy or both at least one year prior to the date of interview; and either no or mild cognitive impairment using the Zambian Mini-Mental Status

Exam (zMMSE). Patients meeting the first two eligibility criteria based on available medical records were approached to complete the zMMSE. The zMMSE is an adapted version of the standard Mini-Mental Status Exam for limited literacy populations. Validated for this setting, a score of 17 is traditionally used as the cut-off for severe cognitive impairment [180,389,390].

Eligible patients were approached for study participation while waiting to be attended to at the clinic. At each of the study sites, patients are seen for their appointment in order of arrival therefore a lengthy wait is often expected. The study consent form was read aloud and discussed with participants before obtaining written, informed consent in the language of their choice (Nyanja, Bemba, or English). All interviews were conducted in private rooms by trained Zambian nurses who were fluent in English as well as multiple local languages. Due to substantial variation in languages, direct translations of study instruments were not prepared. Instead, considerable time was dedicated to ensuring that study staff mastered the content and intent for each item in English so they could be translated for each participant. In exchange for participation, participants were reimbursed 20 kwacha (~4 USD) to cover their transportation to the clinic.

This study was granted ethical approval by the University of Zambia's Biomedical Research Ethics Committee (UNZA BREC) and Michigan State University's Biomedical Institutional Review Board (MSU BIRB).

*Instruments*

The survey instrument was designed for administration via structured interview and included questions regarding: demographic information; educational attainment; employment status; wealth; housing quality; psychiatric morbidity; and personal safety. Wealth was assessed

by enumerating the value of common household items [365,360,174]. Housing quality was assessed using a ranked score based on household construction materials (roof, floor and walls; range 0-15) as well as access to running water and a toilet [360,361,365]. The Shona Symptom Questionnaire (SSQ) was used to assess psychiatric morbidity. Developed in neighboring Zimbabwe [391], the 14-item SSQ has been used successfully in Zambia to query culturally-relevant symptoms of psychological disorders [365,174,241]. Individuals who score greater than 4/14 warrant additional assessment and psychological support [392]. Personal safety was assessed using four questions: history of familial abuse; history of rape (women only); and two questions regarding household cooking and lighting to assess risk of burns.[360,365] Men were not asked about experiences of rape as this inquiry is socially unacceptable in Zambia. As heterosexual transmission is overwhelmingly most common mode of HIV infection in Zambia, participants were not asked about mode of HIV acquisition.

Disease-specific interview questions included: time since diagnosis; disease severity; medication usage; disclosure status; and stigma. For participants with epilepsy, disease severity was ascertained using seizure frequency, time since most recent seizure, and burn scars. For participants with HIV, $CD4^+$ T-cell count was used to assess disease severity. WHO HIV staging was not collected as it is infrequently updated in clinical records and participants rarely recall their stage.

Three instruments were used to assess disease-associated stigma. Each of the stigma instruments are disease-specific and ask participants to report stigmatizing experiences and personal thoughts as they relate to their disease condition, either HIV or epilepsy. Participants with either HIV & epilepsy or epilepsy only, were asked about epilepsy-associated stigma using the Stigma Scale of Epilepsy (SSE) and Jacoby's 3-item Stigma Scale. The SSE is a 24-item

Brazilian instrument with four-point Likert-type responses has been previously validated in Zambia [233]. Jacoby's 3-item Stigma Scale, originally created for stroke patients [236], assesses an individual's perceptions of differential treatment because of their medical condition, and has been used extensively to examine epilepsy stigma, including in Zambia [54,194,190,184,229,393,360,365]. For people with HIV & epilepsy and HIV only, HIV-related stigma was assessed using the HIV/AIDS Stigma Instrument – People Living with HIV/AIDS (HASI-P) and Jacoby's 3-item Stigma Scale. The HASI-P is a 33-item instrument with four-point Likert-type responses that was developed in five neighboring sub-Saharan countries to assess stigma [133]. Jacoby's 3-item Stigma Scale was employed as it is the only instrument that has been previously used to assess HIV-related stigma in Zambia [174]. Participants with HIV & epilepsy were asked Jacoby's 3-item Stigma Scale twice – once with regards to their HIV infection and once with regards to their epilepsy diagnosis.

*Statistical Analysis*

Survey responses were recorded on paper forms before being entered into Microsoft Access, verified for accuracy, and imported into SAS for analysis (version 9.4, SAS, Cary). Stigma scores for each of the stigma instruments were calculated for each individual using recommended procedures. For Jacoby's 3-item Stigma Scale, dichotomous item responses were summed (range 0-3) [54]; for the HASI-P, items were grouped into stigma factors, summed and divided by the number of items in each factor (range for each factor: 0-3) [133]. As previous validation of the SSE in Zambia suggested that the summary score originally proposed by Fernandes et al. [233] may obscure the underlying latent traits assessed by the instrument, IRTPRO (version 2.1, Scientific Software International, Inc, Lincolnwood) was used to calculate

scaled scores for both of the latent traits. Individuals were grouped according to medical condition (epilepsy only, HIV only, or HIV & epilepsy) and group frequencies and means were assessed for categorical and continuous items, respectively. Differences in demographic and clinical characteristics between the three groups were compared using t-tests and $\chi^2$ tests, as appropriate.

Contingency tables were used to assess the association between comorbid HIV and epilepsy and reported HIV-related and epilepsy-associated stigma. It was hypothesized that if layered stigma was present, individuals with comorbid HIV and epilepsy would be more likely to report HIV-related and epilepsy-associated stigma than people with HIV only or epilepsy only, respectively. Likert-type responses for SSE and HASI-P items were dichotomized for comparisons between groups. Potential confounders, such as age, gender, disease severity, and employment, were not addressed due to the small sample size. The relationship between psychiatric morbidity and comorbid HIV and epilepsy was examined by comparing total SSQ scores and the number of individuals needing psychiatric support between groups using $\chi^2$ tests. In addition, because Jacoby's 3-item Stigma Scale, factors associated with the HASI-P and SSE, and SSQ are traditionally treated as continuous measures [365,133,391,394,233], t-tests were also used to compare mean scores to permit comparisons with previously published literature. A p-value of $<0.05$ was considered statistically significant.

**Results**

Between April 17 and December 24, 2013, 101 participants were interviewed to assess layered stigma (20 HIV & Epilepsy, 40 HIV only, and 41 epilepsy only). Sixty-seven participants (66%) were recruited from the adult infectious disease and epilepsy clinics. Of all

individuals approached for participation, eight patients refused (three men with HIV only who had not disclosed their status, three men with epilepsy only who denied their epilepsy diagnosis, and two females with HIV only for unknown reasons). Six individuals were ineligible due to severe cognitive impairment as determined by the zMMSE (four men with epilepsy only, one man with HIV only, and one female with HIV only). Two men with epilepsy only declined to answer most of the stigma questions; therefore, their surveys were discarded.

Table 3.1 shows the demographic and clinical characteristics of each group. Individuals in the HIV only group were older and more likely to be female than individuals in the epilepsy only or HIV & epilepsy groups ($p=0.01$ and $p<0.0001$, respectively). All of the HIV only participants were recruited from the adult infectious disease clinic where this representative of the population served (Personal Communication, L. Mulenga). Participants with HIV only were also more likely to be employed (85% vs. 65% and 39%, $p<0.0001$), whereas participants with epilepsy only were more likely to have a history of familial abuse (20% vs. 5% and 0%, $p=0.005$). Although time since HIV and epilepsy diagnoses was the same between groups, individuals with epilepsy only were diagnosed with epilepsy at a younger age than individuals with HIV and epilepsy (19.5 years vs. 27.1 years, $p=0.04$) and individuals with HIV and epilepsy were diagnosed with HIV at a younger age than individuals with HIV only (32.1 years vs. 37.4 years, $p=0.03$). Severity of HIV infection was the same between the HIV & epilepsy and HIV only groups (CD4: 204 vs. 181 $p=0.70$). However, seizure severity was greater in the HIV & epilepsy group than the epilepsy only group. A greater percentage of individuals in the HIV & epilepsy group had seizures in the previous month than individuals in the epilepsy only group (90% vs. 66% $p=0.04$). Thirteen participants in the epilepsy only group (32%) did not know their HIV status. Of the 20 participants in the HIV & epilepsy group, 15 (75%) were diagnosed

**Table 3.1: Demographic and Clinical Characteristics of Study Population**

| Variable | Epilepsy (n=41) n (%) | HIV (n=40) n (%) | HIV & Epilepsy (n=20) n (%) | P-value |
|---|---|---|---|---|
| *Demographic Characteristics* | | | | |
| Female gender | 16 (39) | 28 (70) | 8 (40) | **0.01** |
| Marital Status | | | | **0.001** |
| Currently married | 12 (29) | 17 (43) | 9 (45) | |
| Never married | 28 (68) | 8 (20) | 8 (40) | |
| Divorced | 1 (2) | 9 (22) | 2 (10) | |
| Widowed | 0 (0) | 6 (15) | 0 (0) | |
| Separated | 0 (0) | 0 (0) | 1 (5) | |
| Currently employed | 16 (39) | 34 (85) | 13 (65) | **<0.0001** |
| Age, mean (SD) | 28.8 (9.9) | 43.2 (9.3) | 37.2 (9.3) | **<0.0001** |
| Years of education, mean (SD) | 8.9 (3.1) | 9.5 (3.7) | 9 (3.3) | 0.69 |
| Housing quality, mean (SD) | 12.3 (0.9) | 12.5 (0.84) | 12.1 (1.02) | 0.32 |
| Household lighting (more than one allowed) | | | | 0.48 |
| Electricity | 35 (80) | 38 (95) | 15 (63) | |
| Kerosene, gas, or paraffin | 2 (5) | 1 (3) | 2 (8) | |
| Candles | 6 14) | 1 (3) | 7 (29) | |
| Solar | 1 (2) | 0 (0) | 0 (0) | |
| Cooking (more than one allowed) | | | | 0.32 |
| Electric stove | 31 (55) | 35 (71) | 14 (47) | |
| Charcoal | 19 (34) | 14 (29) | 15 (50) | |
| Wood | 6 (11) | 0 (0) | 1 (3) | |
| Water Source | | | | 0.18 |
| Running water in home | 17 (42) | 19 (48) | 10 (50) | |
| Community tap | 21 (51) | 13 (33) | 7 (35) | |
| Pump | 2 (5) | 6 (15) | 0 (0) | |
| Well/borehole | 1 (2) | 2 (5) | 3 (15) | |
| Toilet | | | | 0.25 |
| In home | 26 (63) | 31 (80) | 13 (65) | |
| Toilet nearby | 4 (10) | 2 (5) | 3 (15) | |
| Pit latrine | 11 (27) | 6 (15) | 4 (20) | |

**Table 3.1 (cont'd):**

| Variable | Epilepsy (n=41) n (%) | HIV (n=40) n (%) | HIV & Epilepsy (n=20) n (%) | P-value |
|---|---|---|---|---|
| History of Familial Abuse, yes | 8 (20) | 0 (0) | 1 (5) | **0.005** |
| History of Rape, yes (women only) | 0 (0) | 3 (11) | 0 (0) | 0.60 |
| Wealth, USD (SD) | $2,134 (3,674) | $3,3225 (3,116) | $1.909 (1,638) | 0.19 |
| zMMSE score, mean (SD) | 22.5 (2.2) | 23.1 (1.3) | 22.5 (2.0) | 0.24 |
| *HIV Characteristics* | | | | |
| cART, yes | | 40 (100) | 18 (90) | |
| First-line therapy | | 34 (87) | 14 (70) | 0.68 |
| More than once daily dosing, yes | | 18 (46) | 5 (29) | 0.24 |
| Forced disclosure of HIV status, yes | | 2 (5) | 1 (5) | 1.0 |
| Years with HIV, mean (SD) | | 5.8 (3.1) | 5.1 (3.3) | 0.67 |
| Age at HIV diagnosis, mean (SD) | | 37.4 (9.2) | 32.1 (8.3) | **0.03** |
| $CD4^+$ T-cell count, mean (SD) | | 204 (221) | 181 (191) | 0.70 |
| *Epilepsy Characteristics* | | | | |
| Seizure-related burns, yes | 4 (10) | | 2 (10) | 1.0 |
| AED, yes | 41 (100) | | 20 (100) | |
| More than once daily dosing, yes | 7 (17) | | 1 (5) | 0.21 |
| Number of seizures in the past 3 months | | | | 0.11 |
| >1 per week | 2 (5) | | 0 (0) | |
| 1 per week | 4 (10) | | 0 (0) | |
| 1-3 per month | 8 (20) | | 9 (45) | |
| <1 per month | 27 (66) | | 11 (55) | |
| Most recent seizure | | | | **0.04** |
| ≤1 week ago | 12 (29) | | 3 (15) | |
| >1 week ago to ≤1 month ago | 15 (37) | | 15 (75) | |
| >1 month ago to ≤1 year ago | 10 (24) | | 1 (5) | |
| >1 year ago | 4 (10) | | 1 (5) | |
| Forced disclosure of epilepsy, yes | 19 (46) | | 13 (65) | 0.17 |
| Years with epilepsy, mean (SD) | 9.3 (8.2) | | 10.2 (7.6) | 0.76 |
| Age at epilepsy diagnosis, mean (SD) | 19.5 (12.3) | | 27.1 (14.3) | **0.04** |

USD: US Dollars; zMMSE: Zambian Mini-Mental Status Exam; cART: combination antiretroviral therapy; AED: antiepileptic drug

with epilepsy before they were diagnosed with HIV. In addition, 14 (70%) were taking antiepileptic and antiretroviral drug combinations that may affect the therapeutic efficacy of both regimens [353].

Table 3.2 shows responses to HIV-related stigma questions for individuals with both HIV & epilepsy and individuals with HIV only. Generally, few experiences with enacted were reported by either participants with HIV & epilepsy or participants with HIV only. However, both groups reported self-stigmatization due to their HIV diagnosis. Using contingency tables, people in the HIV & epilepsy group were significantly more likely to report feeling that other people blamed them for their HIV status (OR: 5.29 [1.16-24.07]) than people in the HIV only group. People in the HIV & epilepsy group were also significantly more likely to report feeling like they were no longer a person because of their HIV status (OR: 5.29 [1.16-24.07]) than people in the HIV only group. There were no significant differences in overall stigma scores from the HASI-P or Jacoby's 3-item Stigma Scale between the HIV& epilepsy group and HIV only group.

As shown in Table 3.3, reported epilepsy-associated stigma was high for both the HIV & epilepsy group and the epilepsy only group. Comorbid HIV was not significantly associated with increased epilepsy-associated stigma. There were no significant differences in total stigma scores between the HIV & epilepsy group and the epilepsy only group.

Psychiatric morbidity was high in all three groups, with over one-third of participants requiring additional psychiatric assessment and support. As shown in Table 3.4, five participants reported contemplating suicide in the previous week and were given assistance seeking psychiatric care. Comorbid HIV and epilepsy was not associated with increased psychiatric morbidity or need for psychiatric support.

**Table 3.2: Frequencies of HIV-Related Stigma and Association with Layered Stigma**

| HIV/AIDS Stigma Instrument-PLWA | Group | Number (%) | | | | Odds Ratio [CI] |
|---|---|---|---|---|---|---|
| | | No | Yes | | | |
| *In the past 3 months, how often did the following events happen <u>because of your HIV status</u>?* | | *Never* | *Once or twice* | *Several times* | *Most of the time* | |
| 1. I was told to use my own utensils. | HIV | 40 (100) | 0 (0) | 0 (0) | 0 (0) | - |
| | HIV & Epilepsy | 19 (95) | 0 (0) | 1 (5) | 0 (0) | |
| 2. I was asked not to touch someone's child. | HIV | 40 (100) | 0 (0) | 0 (0) | 0 (0) | - |
| | HIV & Epilepsy | 20 (100) | 0 (0) | 0 (0) | 0 (0) | |
| 3. I was made to drink last from the cup. | HIV | 40 (100) | 0 (0) | 0 (0) | 0 (0) | - |
| | HIV & Epilepsy | 20 (100) | 0 (0) | 0 (0) | 0 (0) | |
| 4. Someone mocked me when I passed by. | HIV | 38 (95) | 2 (5) | 0 (0) | 0 (0) | 2.11 [0.26-16.21] |
| | HIV & Epilepsy | 18 (90) | 1 (5) | 1 (5) | 0 (0) | |
| 5. I stopped eating with other people. | HIV | 40 (100) | 0 (0) | 0 (0) | 0 (0) | - |
| | HIV & Epilepsy | 19 (90) | 1 (5) | 0 (0) | 0 (0) | |
| 6. I was asked to leave because I was coughing. | HIV | 40 (100) | 0 (0) | 0 (0) | 0 (0) | - |
| | HIV & Epilepsy | 20 (100) | 0 (0) | 0 (0) | 0 (0) | |
| 7. Someone stopped being my friend. | HIV | 39 (97) | 0 (0) | 1 (3) | 0 (0) | 6.88 [0.67-71.0] |
| | HIV & Epilepsy | 17 (85) | 3 (25) | 0 (0) | 0 (0) | |
| 8. A friend would not chat with me. | HIV | 39 (98) | 0 (0) | 1 (3) | 0 (0) | 2.05 [0.12-34.63] |
| | HIV & Epilepsy | 19 (90) | 1 (5) | 0 (0) | 0 (0) | |
| 9. I was called bad names. | HIV | 34 (85) | 4 (10) | 2 (5) | 0 (0) | 0.3 [0.03-2.67] |
| | HIV & Epilepsy | 19 (95) | 1 (5) | 0 (0) | 0 (0) | |
| 10. People sang offensive songs when I passed by. | HIV | 38 (95) | 1 (3) | 1 (3) | 0 (0) | 1.0 [0.09-11.74] |
| | HIV & Epilepsy | 19 (95) | 1 (5) | 0 (0) | 0 (0) | |
| 11. I was told that I have no future. | HIV | 36 (90) | 3 (8) | 2 (5) | 0 (0) | 1.59 [0.32-7.9] |
| | HIV & Epilepsy | 17 (85) | 3 (15) | 0 (0) | 0 (0) | |
| 12. Someone scolded me. | HIV | 38 (95) | 1 (3) | 1 (3) | 0 (0) | - |
| | HIV & Epilepsy | 20 (100) | 0 (0) | 0 (0) | 0 (0) | |
| 13. I was told that God is punishing me. | HIV | 33 (82) | 5 (13) | 2 (5) | 1 (3) | 0.83 [0.19-3.63] |
| | HIV & Epilepsy | 17 (85) | 2 (10) | 1(5) | 0 (0) | |

**Table 3.2 (cont'd)**

| HIV/AIDS Stigma Instrument-PLWA | Group | Number (%) | | | | Odds Ratio [CI] |
|---|---|---|---|---|---|---|
| | | No | Yes | | | |
| *In the past 3 months, how often did the following events happen <u>because of your HIV status</u>?* | | *Never* | *Once or twice* | *Several times* | *Most of the time* | |
| 14. I was made to eat alone. | HIV | 39 (97) | 1 (3) | 0 (0) | 0 (0) | - |
| | HIV & Epilepsy | 20 (100) | 0 (0) | 0 (0) | 0 (0) | |
| 15. Someone insulted me. | HIV | 37 (92) | 2 (5) | 1 (3) | 0 (0) | 0.65 [0.06-6.67] |
| | HIV & Epilepsy | 19 (95) | 1 (5) | 0 (0) | 0 (0) | |
| 16. People avoided me. | HIV | 36 (90) | 2 (5) | 2 (5) | 0 (0) | 0.47 [0.05-4.54] |
| | HIV & Epilepsy | 19 (95) | 1 (5) | 0 (0) | 0 (0) | |
| 17. People cut down visiting me. | HIV | 35 (87) | 3 (8) | 2 (5) | 0 (0) | 0.37 [0.04-3.39] |
| | HIV & Epilepsy | 19 (95) | 1 (5) | 0 (0) | 0 (0) | |
| 18. People ended their relationships with me. | HIV | 35 (87) | 5 (13) | 0 (0) | 0 (0) | 0.78 [0.14-4.42] |
| | HIV & Epilepsy | 18 (90) | 2 (10) | 0 (0) | 0 (0) | |
| 19. I was blamed for my HIV status. | HIV | 37 (92) | 2 (5) | 1 (3) | 0 (0) | **5.29 [1.16-24.07]** |
| | HIV & Epilepsy | 14 (70) | 6 (30) | 0 (0) | 0 (0) | |
| 20. Someone tried to get me fired from my job. | HIV | 38 (95) | 2 (5) | 0 (0) | 0 (0) | - |
| | HIV & Epilepsy | 20 (100) | 0 (0) | 0 (0) | 0 (0) | |
| 21. My employer denied me opportunities. | HIV | 39 (97) | 0 (0) | 1 (3) | 0 (0) | 2.05 [0.12-34.63] |
| | HIV & Epilepsy | 19 (95) | 0 (0) | 1 (5) | 0 (0) | |
| 22. I was denied health care. | HIV | 39 (97) | 1 (3) | 0 (0) | 0 (0) | - |
| | HIV & Epilepsy | 20 (100) | 0 (0) | 0 (0) | 0 (0) | |
| 23. I was refused treatment because I was told I was going to die anyway. | HIV | 40 (100) | 0 (0) | 0 (0) | 0 (0) | - |
| | HIV & Epilepsy | 20 (100) | 0 (0) | 0 (0) | 0 (0) | |
| 24. I was discharged from the hospital while still needing care. | HIV | 39 (97) | 1 (3) | 0 (0) | 0 (0) | - |
| | HIV & Epilepsy | 20 (100) | 0 (0) | 0 (0) | 0 (0) | |
| 25. I was shuttled around instead of being helped by a nurse. | HIV | 40 (100) | 0 (0) | 0 (0) | 0 (0) | - |
| | HIV & Epilepsy | 20 (100) | 0 (0) | 0 (0) | 0 (0) | |
| 26. At the hospital/clinic, I was made to wait until last. | HIV | 40 (100) | 0 (0) | 0 (0) | 0 (0) | - |
| | HIV & Epilepsy | 20 (100) | 0 (0) | 0 (0) | 0 (0) | |

**Table 3.2 (cont'd)**

| HIV/AIDS Stigma Instrument-PLWA | Group | Number (%) | | | | Odds Ratio [CI] |
|---|---|---|---|---|---|---|
| | | No | Yes | | | |
| *In the past 3 months, how often did the following events happen <u>because of your HIV status</u>?* | | *Never* | *Once or twice* | *Several times* | *Most of the time* | |
| 27. At the hospital, I was left in a soiled bed. | HIV | 40 (100) | 0 (0) | 0 (0) | 0 (0) | - |
| | HIV & Epilepsy | 20 (100) | 0 (0) | 0 (0) | 0 (0) | |
| 28. At the hospital or clinic, my pain was ignored. | HIV | 40 (100) | 0 (0) | 0 (0) | 0 (0) | - |
| | HIV & Epilepsy | 20 (100) | 0 (0) | 0 (0) | 0 (0) | |
| 29. I felt that I did not deserve to live. | HIV | 34 (85) | 3 (7) | 2 (5) | 1 (3) | 1.0 [0.22-4.5] |
| | HIV & Epilepsy | 17 (85) | 2 (10) | 1 (5) | 0 (0) | |
| 30. I felt ashamed of having this disease. | HIV | 30 (75) | 5 (13) | 5 (15) | 0 (0) | 3.0 [0.97-9.3] |
| | HIV & Epilepsy | 10 (50) | 6 (30) | 4 (20) | 0 (0) | |
| 31. I felt completely worthless. | HIV | 36 (90) | 3 (7) | 1 (3) | 0 (0) | 3.86 [0.94-15.76] |
| | HIV & Epilepsy | 14 (70) | 4 (20) | 1 (5) | 1 (5) | |
| 32. I felt that I brought a lot of trouble to my family. | HIV | 27 (67) | 5 (12) | 2 (5) | 1 (3) | 1.7 [0.57-5.11] |
| | HIV & Epilepsy | 11 (55) | 1 (5) | 7 (35) | 1 (5) | |
| 33. I felt that I am no longer a person. | HIV | 37 (92) | 0 (0) | 2 (5) | 1 (3) | **5.29 [1.16-24.07**] |
| | HIV & Epilepsy | 14 (70) | 4 (20) | 2 (10) | 0 (0) | |
| *Scale Factors* | | | | | | P-value |
| Verbal abuse, mean (SD) | HIV | 0.12 (0.32) | | | | 0.962 |
| | HIV & Epilepsy | 0.12 (0.18) | | | | |
| Negative self-perception, mean (SD) | HIV | 0.295 (0.51) | | | | 0.133 |
| | HIV & Epilepsy | 0.53 (0.66) | | | | |
| Healthcare neglect, mean (SD) | HIV | 0.004 (0.022) | | | | 0.484 |
| | HIV & Epilepsy | 0 (0) | | | | |
| Social isolation, mean (SD) | HIV | 0.11 (0.32) | | | | 0.652 |
| | HIV & Epilepsy | 0.08 (0.18) | | | | |
| Fear of contagion, mean (SD) | HIV | 0.008 (0.05) | | | | 0.398 |
| | HIV & Epilepsy | 0.026 (0.08) | | | | |

**Table 3.2 (cont'd)**

| **HIV/AIDS Stigma Instrument-PLWA** | **Group** | **Number (%)** | | | | **Odds Ratio [CI]** |
|---|---|---|---|---|---|---|
| | | **No** | **Yes** | | | |
| *In the past 3 months, how often did the following events happen <u>because of your HIV status</u>?* | | *Never* | *Once or twice* | *Several times* | *Most of the time* | |
| Workplace stigma, mean (SD) | HIV | 0.05 (0.24) | | | | 1.0 |
| | HIV & Epilepsy | 0.05 (0.22) | | | | |
| *3-Item Stigma Scale* | *Group* | *Number (%)* | | | | |
| Because of my HIV: | | | | | | |
| I feel that some people are uncomfortable with me, yes | HIV | 6 (15) | | | | 1.0 [0.22-4.5] |
| | HIV & Epilepsy | 3 (15) | | | | |
| I feel some people treat me like an inferior person, yes | HIV | 2 (5) | | | | 4.75 [0.79-28.6] |
| | HIV & Epilepsy | 4 (20) | | | | |
| I feel some people would prefer to avoid me, yes | HIV | 1 (3) | | | | 2.05 [0.12-34.6] |
| | HIV & Epilepsy | 1 (5) | | | | |
| 3-Item Stigma Scale Score | | Number (%) | | | | *Odds Ratio [CI]* |
| 0 | HIV | 34 (85) | | | | 2.43 [0.78-8.84] |
| | HIV & Epilepsy | 14 (70) | | | | |
| 1 | HIV | 4 (10) | | | | |
| | HIV & Epilepsy | 4 (20) | | | | |
| 2 | HIV | 1 (2.5) | | | | |
| | HIV & Epilepsy | 2 (3.3) | | | | |
| 3 | HIV | 1 (2.5) | | | | |
| | HIV & Epilepsy | 0 (0) | | | | |
| Mean 3-item Stigma Score | HIV | 0.225 (0.62) | | | | p=0.322 |
| | HIV & Epilepsy | 0.40 (0.68) | | | | |

**Table 3.3: Reported Epilepsy-Associated Stigma and Association with Layered Stigma**

| | Group | Number (%) | | | | Odds Ratio [CI] |
|---|---|---|---|---|---|---|
| | | No | Yes | | | |
| *Stigma Scale of Epilepsy* | | *Not at all* | *A Little* | *A Lot* | *Totally* | |
| Do you think that people with epilepsy feel able to control their own epilepsy?[bb] | Epilepsy | 27 (66) | 3 (7) | 3 (7) | 8 (20) | 0.57 [0.17-19.3] |
| | HIV & Epilepsy | 12 (60) | 1 (5) | 1 (5) | 6 (30) | |
| How would you feel when you see an epileptic seizure? Scared | Epilepsy | 15 (37) | 5 (12) | 13 (32) | 8 (20) | 2.31 [0.65-8.19] |
| | HIV & Epilepsy | 4 (20) | 4 (20) | 6 (30) | 6 (30) | |
| How would you feel when you see an epileptic seizure? Fear | Epilepsy | 10 (24) | 6 (15) | 19 (46) | 6 (15) | 2.9 [0.57-14.75] |
| | HIV & Epilepsy | 2 (10) | 3 (15) | 14 (70) | 1 (5) | |
| How would you feel when you see an epileptic seizure? Sadness | Epilepsy | 7 (17) | 3 (7) | 11 (27) | 20 (49) | 1.85 [0.35-9.86] |
| | HIV & Epilepsy | 2 (10) | 1 (5) | 3 (15) | 14 (70) | |
| How would you feel when you see an epileptic seizure? Pity | Epilepsy | 9 (22) | 4 (10) | 9 (22) | 19 (46) | 5.34 [0.63-45.53] |
| | HIV & Epilepsy | 1 (5) | 0 (0) | 6 (30) | 13 (65) | |
| Which difficulties do you think people with epilepsy have in their daily lives? Relationships | Epilepsy | 17 (42) | 4 (10) | 17 (42) | 3 (7) | 1.65 [0.53-5.17] |
| | HIV & Epilepsy | 6 (30) | 3 (15) | 8 (40) | 3 (15) | |
| Which difficulties do you think people with epilepsy have in their daily lives? Work | Epilepsy | 17 (42) | 9 (22) | 8 (20) | 7 (17) | 2.83 [0.80-9.98] |
| | HIV & Epilepsy | 4 (20) | 2 (10) | 3 (15) | 11 (55) | |
| Which difficulties do you think people with epilepsy have in their daily lives? School | Epilepsy | 11 (28) | 2 (5) | 11 (28) | 16 (40) | 0.49 [0.12-1.97] |
| | HIV & Epilepsy | 3 (16) | 2 (11) | 2 (11) | 12 (63) | |
| Which difficulties do you think people with epilepsy have in their daily lives? Friendships | Epilepsy | 20 (49) | 6 (15) | 12 (29) | 3 (7) | 0.86 [0.29-2.51] |
| | HIV & Epilepsy | 9 (45) | 4 (20) | 5 (25) | 2 (10) | |
| Which difficulties do you think people with epilepsy have in their daily lives? Sexual | Epilepsy | 20 (49) | 6 (15) | 7 (17) | 8 (20) | 1.95 [0.65-5.88 |
| | HIV & Epilepsy | 13 (65) | 1 (5) | 4 (20) | 2 (10) | |

[bb] Response categories were inverted for analysis ("Totally"=No, whereas "Not at all", "A little", & "A lot" = Yes)

**Table 3.3 (cont'd)**

| | Group | Number (%) | | | | Odds Ratio [CI] |
|---|---|---|---|---|---|---|
| | | No | Yes | | | |
| *Stigma Scale of Epilepsy* | | *Not at all* | *A Little* | *A Lot* | *Totally* | |
| Which difficulties do you think people with epilepsy have in their daily lives? Emotional | Epilepsy | 14 (34) | 6 (15) | 11 (27) | 10 (24) | 0.64 [0.19-2.14] |
| | HIV & Epilepsy | 5 (25) | 3 (15) | 4 (20) | 8 (40) | |
| Which difficulties do you think people with epilepsy have in their daily lives? Prejudice | Epilepsy | 19 (48) | 11 (28) | 8 (20) | 2 (5) | 2.15 [0.71-6.49] |
| | HIV & Epilepsy | 13 (65) | 5 (25) | 1 (5) | 1 (5) | |
| How do you think that people with epilepsy feel? Worried | Epilepsy | 6 (15) | 2 (5) | 24 (59) | 9 (22) | 0.97 [0.22-4.36] |
| | HIV & Epilepsy | 3 (15) | 1 (5) | 11 (55) | 5 (25) | |
| How do you think that people with epilepsy feel? Dependent | Epilepsy | 10 (25) | 6 (15) | 7 (17) | 18 (44) | 1.83 [0.44-7.56] |
| | HIV & Epilepsy | 3 (15) | 2 (10) | 4 (20) | 11 (55) | |
| How do you think that people with epilepsy feel? Incapable | Epilepsy | 8 (20) | 8 (20) | 10 (25) | 14 (35) | 0.73 [0.20-2.6] |
| | HIV & Epilepsy | 5 (25) | 3 (15) | 6 (30) | 6 (30) | |
| How do you think that people with epilepsy feel? Fearful | Epilepsy | 12 (29) | 3 (7) | 19 (46) | 7 (17) | 2.35 [0.58-9.51] |
| | HIV & Epilepsy | 3 (15) | 2 (10) | 8 (40) | 7 (35) | |
| How do you think that people with epilepsy feel? Depressed | Epilepsy | 7 (17) | 7 (17) | 6 (16) | 21 (51) | 1.17 [0.27-5.09] |
| | HIV & Epilepsy | 3 (15) | 0 (0) | 5 (25) | 12 (60) | |
| How do you think that people with epilepsy feel? Ashamed | Epilepsy | 12 (29) | 5 (12) | 10 (24) | 14 (34) | 0.6 [0.17-2.2] |
| | HIV & Epilepsy | 4 (20) | 2 (10) | 4 (20) | 10 (50) | |
| How do you think that people with epilepsy feel? The same as those without epilepsy[cc] | Epilepsy | 22 (55) | 3 (8) | 3 (8) | 12 (30) | 2.35 [0.58-9.51] |
| | HIV & Epilepsy | 14 (70) | 2 (10) | 1 (5) | 3 (15) | |
| In your opinion, the prejudice in epilepsy will be related to? Relationships | Epilepsy | 12 (30) | 8 (20) | 19 (48) | 1 (3) | 1.3 [0.42-4.07] |
| | HIV & Epilepsy | 7 (35) | 2 (10) | 8 (40) | 3 (15) | |
| In your opinion, the prejudice in epilepsy will be related to? Marriage | Epilepsy | 21 (55) | 7 (18) | 7 (18) | 3 (8) | 0.64 [0.22-1.88] |
| | HIV & Epilepsy | 8 (42) | 7 (37) | 4 (21) | 0 (0) | |
| In your opinion, the prejudice in epilepsy will be related to? Work | Epilepsy | 14 (36) | 9 (23) | 7 (18) | 9 (23) | 1.56 [0.47-5.17] |
| | HIV & Epilepsy | 5 (25) | 3 (15) | 10 (50) | 2 (10) | |

[cc] Response categories were inverted for analysis ("Totally"=No, whereas "Not at all", "A little", & "A lot" = Yes)

**Table 3.3 (cont'd)**

| | Group | Number (%) | | | | Odds Ratio [CI] |
|---|---|---|---|---|---|---|
| | | No | Yes | | | |
| In your opinion, the prejudice in epilepsy will be related to? School | Epilepsy | 6 (16) | 6 (16) | 10 (26) | 16 (42) | 0.32 [0.09-1.13] |
| | HIV & Epilepsy | 7 (35) | 2 (10) | 3 (15) | 8 (40) | |
| In your opinion, the prejudice in epilepsy will be related to? Family | Epilepsy | 27 (69) | 7 (18) | 3 (8) | 2 (5) | 0.48 [0.14-1.72] |
| | HIV & Epilepsy | 16 (60) | 2 (10) | 1 (5) | 1 (5) | |
| *Scale Factors* | | | | | | *P-value* |
| Fear of encountering stigma, mean (SD) | Epilepsy | 2.11 (0.78) | | | | 0.381 |
| | HIV & Epilepsy | 2.32 (0.94) | | | | |
| Negative self-perception, mean (SD) | Epilepsy | 2.58 (0.82) | | | | 0.112 |
| | HIV & Epilepsy | 2.94 (0.82) | | | | |
| *3-Item Stigma Scale* | *Group* | *Number (%)* | | | | *OR [CI]* |
| Because of my Epilepsy: | | | | | | |
| I feel that some people are uncomfortable with me, yes | Epilepsy | 17 (42) | | | | 0.94 [0.32-2.79] |
| | HIV & Epilepsy | 8 (40) | | | | |
| I feel some people treat me like an inferior person, yes | Epilepsy | 13 (32) | | | | 1.44 [0.63-4.36] |
| | HIV & Epilepsy | 8 (40) | | | | |
| I feel some people would prefer to avoid me, yes | Epilepsy | 9 (22) | | | | 2.37 [0.74-7.57] |
| | HIV & Epilepsy | 8 (40) | | | | |
| *3-Item Stigma Scale Score* | | | | | | *OR [CI]* |
| 0 | Epilepsy | 21 (51) | | | | 1.28 [0.44-3.75] |
| | HIV & Epilepsy | 9 (45) | | | | |
| 1 | Epilepsy | 9 (22) | | | | |
| | HIV & Epilepsy | 3 (15) | | | | |
| 2 | Epilepsy | 3 (7) | | | | |
| | HIV & Epilepsy | 3 (15) | | | | |
| 3 | Epilepsy | 8 (20) | | | | |
| | HIV & Epilepsy | 5 (25) | | | | |
| Mean Stigma Score (SD) | Epilepsy | 0.95 (1.18) | | | | p=0.46 |
| | HIV & Epilepsy | 1.2 (1.28) | | | | |

**Table 3.4: Psychiatric Morbidity by Comorbid Illness**

| **Shona Symptom Questionnaire (SSQ)** | **Epilepsy (n=41) n (%)** | **HIV (n=40) n (%)** | **HIV & Epilepsy (n=20) n (%)** |
|---|---|---|---|
| During the course of the past week: | | | |
| Did you have times in which you were thinking deeply or thinking about many things?, yes | 26 (63) | 21 (53) | 13 (65) |
| Did you find yourself sometimes failing to concentrate?, yes | 23 (56) | 16 (40) | 11 (55) |
| Did you lose your temper or get annoyed over trivial matters?, yes | 16 (39) | 15 (38) | 3 (15) |
| Did you have nightmares or bad dreams?, yes | 10 (24) | 5 (12.5) | 4 (20) |
| Did you sometimes see or hear things which others could not see or hear?, yes | 6 (15) | 1 (2.5) | 1 (5) |
| Was your stomach aching?, yes | 11 (27) | 13 (33) | 6 (30) |
| Were you frightened by trivial things?, yes | 2 (5) | 4 (10) | 1 (5) |
| Did you sometimes fail to sleep or lose sleep?, yes | 11 (27) | 20 (50) | 5 (25) |
| Were there moments when you felt life was so tough that you cried or wanted to cry?, yes | 22 (54) | 21 (53) | 11 (55) |
| Did you feel run down (tired)?, yes | 10 (24) | 17 (43) | 4 (20) |
| Did you at times feel like committing suicide?, yes | 3 (7) | 3 (7) | 1 (5) |
| Were you generally unhappy with things you were doing each day?, yes | 11 (27) | 7 (18) | 5 (25) |
| Was your work lagging behind?, yes | 17 (42) | 8 (20) | 5 (25) |
| Did you feel you had problems in deciding what to do?, yes | 14 (34) | 13 (33) | 7 (35) |

| *SSQ Score* | Epilepsy (n=41) | HIV (n=40) | HIV & Epilepsy (n=20) | *p-value* |
|---|---|---|---|---|
| Mean score (SD) | 4.4 (3.1) | 4.1 (3.0) | 3.85 (2.6) | 0.781 |
| Needing psychiatric support, yes[dd] n (%) | 17 (42) | 14 (35) | 7 (35) | 0.792 |

[dd] SSQ Score ≥5

**Discussion**

Disease-associated stigma is widely considered one of the most enduring barriers to ameliorating the burden of conditions like HIV and epilepsy [107,30]. As HIV-positive individuals in developing countries continue to live longer due to increased availability of antiretroviral drugs, the likelihood that they will have a stigmatized comorbid condition will increase substantially. Despite this, investigation into the characteristics of individuals with comorbid stigmatized conditions as well as their experiences with layered stigma are limited. In this study, people with HIV only were more likely to be older and female than people with HIV and epilepsy or epilepsy only (all $p<0.01$). As previously reported in Zambia, a diagnosis of epilepsy in our study was associated with decreased marriage and employment (both $p<0.001$) [360]. Individuals with comorbid HIV and epilepsy in this study were older when they were diagnosed with epilepsy than individuals with epilepsy only ($p=0.04$), yet they were younger when diagnosed with HIV than individuals with HIV only ($p=0.03$). This supports previous findings in Zambia that people with epilepsy are a vulnerable population [184,395]. In addition, people with HIV and epilepsy were more likely to have a seizure in the previous month than people with epilepsy only ($p=0.04$). Insufficient seizure control in individuals with comorbid HIV and epilepsy may be a result of more severe underlying disease etiology or antiepileptic drug treatment failure due to interactions with antiretroviral drugs [353]. This deserves further investigation. As 75% of people with comorbid HIV and epilepsy were diagnosed with epilepsy prior to HIV, antiepileptic drug failure may be more likely cause of more frequent seizures than disease etiology.

This study suggests that comorbid epilepsy is modestly associated with higher reported HIV-related stigma. People with HIV and epilepsy were significantly more likely to report

feeling like they were blamed by other people for their HIV status than people with HIV only. They were also more likely to feel like they were no longer a person. Unfortunately, because the stigma instruments that have been validated in this setting are disease-specific, we were unable to determine whether layered stigma from comorbid HIV and epilepsy is additive or multiplicative as not all participants could be asked all of the stigma questions. We were also unable to control for potential confounders, such as gender, age, employment, and disease severity, due to our small sample size.

Comorbid HIV and epilepsy was not associated with increased reporting of epilepsy-associated stigma. This may be related to the order of diagnoses for people with HIV and epilepsy included in this study. As the majority were diagnosed with epilepsy prior to HIV, they may be sensitized to HIV-related stigma in a way that people in the HIV only group are not. As a result, they may attribute discrimination from unaffected individuals to their recent HIV diagnoses, even when the discrimination is a manifestation of epilepsy-associated enacted stigma. Future research should examine the impact of the order of diagnoses on layered stigma.

The prevalence of HIV-related and epilepsy-associated stigma among individuals with HIV only and epilepsy only was similar to previous studies in this setting [174,365]. Despite our small sample size and the fact that the instruments employed were not designed for layered stigma, significant differences were noted in reported HIV-related stigma. Although differences were not found in epilepsy-associated stigma or psychiatric morbidity, the emotional burden of epilepsy was still apparent. Two women with HIV and epilepsy cried during their interviews.

The external validity of this study is potentially limited. Because study participants were recruited from health care facilities, they are not a representative sample of all people with HIV and epilepsy due to the sizable treatment gap for both conditions in Zambia [27,7]. Study

participants may be healthier and less stigmatized than individuals with the same diagnoses who do not have access to HIV or epilepsy care. In addition, the extent of enacted stigma that participants reported experiencing in health care settings on the HASI-P may have also been underestimated as the interviews were conducted in clinics by health care personnel.

Although layered stigma is often overlooked, this study suggests that it may be responsible for some of the variation in disease-associated stigma reported by affected individuals. If not addressed, layered stigma may adversely impact the effectiveness of stigma interventions. Additional investigations into layered stigma leading to the development of instruments to examine stigma resulting from comorbid medical conditions such as HIV and epilepsy are warranted.

# CHAPTER 4:

# ADVERSE EVENTS ASSOCIATED WITH PHENOBARBITAL USAGE AMONG PEOPLE WITH EPILEPSY IN ZAMBIA


## Abstract

*Objective*

Phenobarbital is one of the most widely used antiepileptic drugs worldwide, yet there are limited data regarding the occurrence of adverse events associated with its use, particularly in routine clinical care settings in low-income countries. Available data suggests that phenobarbital is as effective as other first-line AEDs for treating tonic-clonic seizures, but reports of adverse events differ widely between high and low-income settings. A more complete understanding of the adverse events of phenobarbital is warranted to allow for safe use in an effort to decrease the epilepsy treatment gap in low-income settings

*Methods*

We used the Liverpool Adverse Events Profile (LEAP) to assess adverse events in people taking phenobarbital to manage recurrent seizures in rural Zambia. Data regarding age, gender, medication dose, and medication adherence were also collected. T-tests and Spearman's correlation coefficient were used to assess predictors of total side effects score and medication adherence.

*Results*

Thirty-five people with epilepsy had obtained phenobarbital as part of their routine clinical care (mean dose: 2.1 mg/kg/day). All participants reported at least one adverse event in the previous four weeks. People taking phenobarbital reported a mean of 5 symptoms and a mean side effects score of 28/76. Over half reported sleepiness and dizziness. Memory problems and depression were also common (both 46%). Total side effects score was not associated with age ($p=0.88$), gender ($p=0.17$), or phenobarbital dose ($p=0.13$). Medication adherence was not associated with side effects total score ($p=0.56$).

*Conclusions*

Adults taking phenobarbital at doses recommended by the WHO for seizure management in rural Zambia report a significant number of medication side effects. The most common side effects reported were similar to the side effects reported by people taking phenobarbital in high-income countries. The high rate of adverse events in this cohort is in contrast to data from non-randomized clinical trials in low-income settings that report that phenobarbital is well-tolerated. Additional investigation into adverse events among patients obtaining phenobarbital as part of routine clinical care in low income settings is warranted.

## Introduction

One hundred years after its introduction, phenobarbital continues to be one of the most widely used antiepileptic drugs (AED) worldwide [396]. In high-income countries, phenobarbital has been replaced by newer AEDs that have fewer reported adverse events [397]. Due to its minimal cost, convenient dosing, and broad spectrum of activity, the World Health Organization continues to recommend phenobarbital as first-line monotherapy for seizure treatment in resource-limited settings [300]. The cost advantages of phenobarbital over other first generation AEDs are substantial. In Zambia, where most people live on less than two United States Dollars (USD) per day, the monthly out-of-pocket cost for phenobarbital in the private sector is about nine USD, which is half the cost of phenytoin and one third the cost of valproic acid. In the public sector phenobarbital costs even less, with wholesale costs for adult dosing being less than a dollar a month [303].

Research from low and high-income settings has shown that phenobarbital is as effective as other first-line AEDs for tonic-clonic seizure control [398,399,311,400-403]. However, data regarding adverse events is less clear. Meta-analyses suggest that phenobarbital is more likely to be withdrawn due to side effects than carbamazepine, phenytoin, or valproic acid [398,399,404] and that people taking phenobarbital monotherapy experience more frequent/severe side effects than people taking carbamazepine [405,324,406,194], phenytoin [407], valproic acid [408,407,194], or placebo [409] in high-income settings. Yet, in low-income settings, observational studies suggest that phenobarbital is well tolerated [331,330,329] and, as shown in Table 4.1, randomized trials have shown mixed results when compared to other first-line AEDs [402,410,411,403,412,311]. Conflicting findings regarding phenobarbital tolerability have been largely attributed to substantial heterogeneity between studies [398,404]. Assessment of

**Table 4.1: Studies Examining Phenobarbital-Related Adverse Events**

| Year | Authors | Patient Population | AEDs | Adverse Events Assessment | Findings |
|---|---|---|---|---|---|
| 1979 | Camfield et al. [409] | 6 months-3 years old with febrile seizure (Canada) | 35 PB (4-5 mg/kg/day OD) vs 30 Placebo, randomized | Query parents about sleep disturbances, behavioral change & hyperactivity. Bayley Scales of Infant Development or Stanford Binet Intelligence Scale. | Dose-related and unacceptable side effects greater in PB group. Decreased memory concentration tasks and decreased lower general comprehension over time in PB group. |
| 1985<br><br><br>1987 | Mattson et al. [316]<br>Smith et al. [405] | Adults with seizures, Veterans Administration Epilepsy Cooperative Group (USA) | 101 CBZ, 101 PB, 110 PHT, 109 PRM, doses unknown, randomized | Rating scales for systemic toxicity, neurotoxicity | CBZ had fewest side effects. |
| 1987 | Vining et al. [408] | Children with mild seizure disorders (USA) | 21 children, PB (3.4mg/kg/day) & VA (27.2 mg/kg/day), crossover 6 months on each, one month washout | Continuous Performance Reaction Test, Abbot Parent and teacher Questionnaires for emotional and behavioral side effects. History and physical assessment for side effects | Increased disobedience, psychosomatic pain, ataxia, gastrointestinal disturbances, hyperactivity, unhappiness, anxiety, problems with peers, sleep problems, and decreased concentration and reaction time when on PB. |
| 1988 | Herranz et al. [324] | Pediatric outpatients with seizures (Spain) | 99 PB (4-6 mg/kg/day), 85 PRM (15-20 mg/kg/day), 63 PHT (8-12 mg/kg/day), 35 CBZ (20-25 mg/kg/day) 110 VA (30-40mg/kg/day), not randomized | Clinical exam and patient/family report | CBZ most tolerable drug, Behavioral problems most common in PB group. |

CBZ: Carbamazepine; PB: Phenobarbital; PHT: phenytoin; PRM: primidone VA: valproic acid

**Table 4.1 (cont'd)**

| Year | Authors | Patient Population | AEDs | Adverse Events Assessment | Findings |
|---|---|---|---|---|---|
| 1989 | Tedeshi et al. [406] | Patients with epilepsy (Italy) | 20 CBZ monotherapy, 12 PB monotherapy, 12 CBZ+PB, non-randomized, 20 healthy controls | Saccadic Eye Movements Analysis | All groups impaired compared to controls. PB group had greater sedative effect. |
| 1991 | Feksi et al. [402] | Age 6-65 years with tonic-clonic seizures (Kenya) | 152 CBZ, 150 PB, doses unknown, randomized | Checklist | More reports of adverse effects with PB than CBZ (specific effects not provided). |
| 1993 | Placencia et al. [410] | Age 2-60 years with tonic-clonic seizures (Ecuador) | 97 PB, 95 CBZ, doses unknown, randomized | Checklist | No difference in side effects between groups (specific effects not provided). |
| 1995 | Heller et al. [401] | Over 16 years with untreated seizures (UK) | 58 PB, 63 PHT, 61 CBZ, 61 VA, doses unknown | Not stated | More likely to have drug withdrawn due to unacceptable side effects in PB group. |
| 1995 | Meador et al. [407] | Healthy adults (USA) | Crossover design: 12 PB/PHT, 12 PHT/PB, 13 PB/VA, 12 VA/PB, 13 PHT/VA, 13 VA/PHT | Neurobehavioral battery | Worse performance on PB across all groups. |
| 1996 | Chen et al. [411] | 7-15 years with new-onset epileptic seizures (China) | 26 CBZ, 25 PB or 25 VA, doses unknown, randomized | Weschler Intelligence Scale for Children-Revised, Bender-Gestalt test | Decreased cognitive function in PB group. |
| 1996 | De Silva et al. [400] | 3-16 years with tonic-clonic or partial seizures(UK) | 10 PB, 54 PHT, 54 CBZ, 49 SA, randomized | Not described | PB group halted after 10 children enrolled due to side effects in 6. |

CBZ: Carbamazepine; PB: Phenobarbital; PHT: phenytoin; PRM: primidone VA: valproic acid

**Table 4.1 (cont'd)**

| Year | Authors | Patient Population | AEDs | Adverse Events Assessment | Findings |
|---|---|---|---|---|---|
| 1996 | Thilotha-mmal et al. [403] | 4-12 years with generalized tonic-clonic seizures (India) | 51 PB (3-5 mg/kg/day) 52 PHT (5-8 mg/kg/day), 48 VA 15-50 mg/kg/day), randomized | Clinical examination | Most side effects in PHT group than PB group than VA group.<br>More than one side effect in 32% of PB group. |
| 1997 | Baker et al. [194] | Adults >16 years with epilepsy (Sweden, Italy, Spain, Germany, Netherlands, UK, France, Switzerland) | 112 PB, 387 PHT, 556 VA, 994 CBZ, doses not provided, not randomized | Liverpool Adverse Events Profile | PB group showed greater restlessness, trouble with mouth/gums, disturbed sleep, than VA and CBZ group, greater nervousness/agitation than CBZ group, greater upset stomach, weight gain, than PHT and CBZ |
| 1998 | Pal et al.[412] | 2-18 years with partial and generalized tonic-clonic seizures (India) | 47 PB (3.0 mg/kd/day), 47 PHT (5.0 mg/kd/day), randomized | Conners parent rating scale (>6 years) or Preschool Behavior Screening Questionnaire (2-5 years) | No difference in parental report of behavior problems. |

CBZ: Carbamazepine; PB: Phenobarbital; PHT: phenytoin; PRM: primidone VA: valproic acid

treatment-related adverse events is often a secondary outcome and, as a result, little detail is provided regarding the instruments used to measure side effects. Also often overlooked is the potential for disparate presentation of complaints based on study participants' culture [413-415] as well as for acceptance and minimization of adverse events due to limited alternative therapies [333,330,416]. As most data collected in low-income settings are associated with efforts to provide seizure treatment to populations residing in areas where it was otherwise unavailable, inadvertent overestimation of phenobarbital tolerability may have occurred [404].

Previous research in upper-middle and high-income settings suggests that people obtaining AED therapy continue to report adverse events even after seizure control is established [417-419]. Unfortunately, there are limited data regarding adverse events among individuals provided phenobarbital outside of research studies in low-income settings. In order to examine the frequency/severity of reported adverse events among people with epilepsy obtaining phenobarbital as part of routine clinical care in a resource-limited setting, we assessed the side effects of phenobarbital use in rural Zambia using a standard adverse events reporting instrument. All participants were people with epilepsy on a stable dose of phenobarbital for at least two months prior to assessment. We also examined predictors of phenobarbital-related side effects and medication adherence.

**Methods**

Consecutive patients presenting for care to Chikankata Hospital Epilepsy Care Team (ECT) who met the study inclusion criteria and consented to participate were interviewed regarding AED side effects during the month of January 2006. Chikankata Hospital is a mission hospital that provides the only source of health care for a catchment area of approximately

55,000 people in an isolated region of the rural Southern Province. The ECT consists of a neurologist who is in residence, on average, six months a year; a clinical officer; a ward auxiliary; and a research assistant/administrator. At the time of survey, phenobarbital was the most widely available AED and was provided at no cost to the patient. Carbamazepine and phenytoin were available as second line treatment at low cost, but both agents were infrequently used at the time since they were in very limited supply.

Individuals were eligible for study inclusion if they were at least 18 years old, had been taking a stable dose of an AED for at least two months, and were able to answer questions in either Tonga (the local language) or English. Written, informed consent was obtained from each participant in the language of his/her choice. AED-related side effects were ascertained using the Liverpool Adverse Events Profile (LEAP) [420]. This 19-item instrument queries the severity of common AED side effects during the four weeks prior to interview. Participant responses are coded using Likert-type scales (from 0-3), three representing a symptom that occurs "often". A total side effect score can be calculated by summing participant responses (range 0-57), although concern has been raised that this may obscure individual complaints [421]. The LEAP was translated into Tonga and then back-translated to ensure content validity.

Data was also collected regarding: participant's gender, age, and weight. To assess AED adherence, the following were abstracted from the patient file: AED name, dose, number of pills collected, and the date phenobarbital was last collected from the pharmacy. Patient self-report of last phenobarbital dose taken was also obtained. Patients were deemed adherent if they had taken their medication either the day prior to or the day of their appointment and if pharmacy data reflected that they were not overdue on medication collection. This approach has been used to assess adherence in this setting previously as laboratory facilities for serum concentrations are

not available [365,174]. ECT staff collected data via structured interview. Previous research at this site suggests that patients are comfortable confiding in the ECT research assistants as they are respected members of the community but do not hold positions of tribal or local governmental authority.

Summary statistics were performed for all interviewed patients. To assess predictors of phenobarbital-related side effects, two-tailed comparisons were made between total side effects score for participants taking phenobarbital and gender, age, and phenobarbital dose using t-tests and spearman's correlation coefficient, as appropriate. T-tests were also used to examine the effect of total side effect score on medication adherence. A p-value of $<0.05$ was considered statistically significant. SAS (version 9.4, SAS Institute Inc., Cary) was used for all data analysis.

Prior to study initiation, ethical approval was obtained from Michigan State University's Biomedical Institutional Review Board (MSU BIRB) and the University of Zambia's Biomedical Research Ethics Committee (UNZA BREC).

**Results**

Thirty-nine people with epilepsy (18 female, 46%) were interviewed during the study period. Ninety percent (39/43) of individuals approached agreed to participate. Reasons for refusal were not collected. The mean age of participants was 26.4 years (SD 10.4 years). At the time of interview, 35 participants were taking phenobarbital, three were taking carbamazepine, and one was taking phenytoin. AED adherence was generally high. Twenty-nine participants (85%) had not missed a dose of their AED; only two had not taken their AED in more than one week (6%). The mean daily dose of phenobarbital was 2.1 mg/kg/day.

All participants reported at least one side effect in the four weeks prior to interview. Participants taking phenobarbital endorsed, on average, five symptoms (range 1-12). As shown in Table 4.2, among individuals taking phenobarbital, the most commonly endorsed side effects were sleepiness (74%), dizziness (60%), memory problems (46%) and depression (46%). No participants experienced alopecia. Eleven participants (31%) reported at least one symptom "often" in the previous four weeks. Total side effects scores for participants taking phenobarbital ranged from 19-28 with a mean score of 22.57 (SD 2.85).

**Table 4.2: Adverse Events Reported by People Taking Phenobarbital, Number (%) (n=35)**

| | Never | Rarely | Sometimes | Often |
|---|---|---|---|---|
| Ataxia | 28 (80) | 4 (11) | 2 (6) | 1 (3) |
| Tiredness | 25 (72) | 6 (17) | 4 (11) | 0 (0) |
| Restless | 26 (74) | 8 (23) | 1 (3) | 0 (0) |
| Feelings of aggression | 21 (60) | 7 (20) | 5 (14) | 2 (6) |
| Nervousness | 24 (69) | 6 (17) | 5 (14) | 0 (0) |
| Headache | 25 (71) | 3 (9) | 7 (20) | 0 (0) |
| Hair loss | 35 (100) | 0 (0) | 0 (0) | 0 (0) |
| Problems with skin | 33 (94) | 1 (3) | 1 (3) | 0 (0) |
| Double/blurred vision | 29 (83) | 4 (11) | 2 (6) | 0 (0) |
| Upset stomach | 23 (66) | 6 (17) | 4 (11) | 2 (6) |
| Difficulty concentrating | 21 (60) | 7 (20) | 5 (14) | 2 (6) |
| Trouble with mouth or gums | 33 (94) | 0 (0) | 2 (6) | 0 (0) |
| Tremor | 28 (80) | 5 (14) | 2 (6) | 0 (0) |
| Weight gain[ee] | 33 (94) | 1 (3) | 0 (0) | 0 (0) |
| Dizziness | 14 (40) | 9 (26) | 8 (23) | 4 (11) |
| Sleepiness | 9 (26) | 6 (17) | 13 (37) | 7 (20) |
| Depression | 19 (54) | 9 (26) | 5 (14) | 2 (6) |
| Memory Problems | 19 (54) | 5 (14) | 8 (23) | 3 (9) |
| Disturbed sleep | 24 (69) | 6 (17) | 3 (9) | 2 (6) |

[ee] Missing response for 1 participant (3%)

Greater phenobarbital-related total side effects score was not related to age (p=0.717), gender (p=0.077), or dose (p=0.679). Medication adherence was not associated with side effects total score (22.72 vs 22.0, p=0.611). A *post hoc* power analysis indicated that with 35 participants, we had 80% power to detect an association between medication adherence with a difference in mean side effects total score of 2.82 (σ=2.85).

**Discussion**

Although the data presented here is from a convenience sample, the findings are interesting. Adults obtaining phenobarbital as part of routine clinical care in rural Zambia at a mean dose falling within WHO recommendations (1-3 mg/kg/day) [300] reported a significant number of adverse events. All participants reported at least one adverse event in the previous four weeks. The symptoms reported with the greatest frequency are similar to the symptoms most frequently reported by people with epilepsy taking phenobarbital in high-income settings [194]. Adverse events were ubiquitous in our study sample; they were not associated with age, gender, or phenobarbital dose.

The number of Zambian people with epilepsy reporting adverse events in this study is substantially higher than the number of phenobarbital-related side effects previously reported in low-income settings. As direct inquiry has been associated with increased side effects reporting, Zambian people with epilepsy may have endorsed a greater number of adverse events than participants in a study in China, even though there was little difference in total daily dose of phenobarbital (Zambia: 107mg, China: 120mg) [329], because we inquired about more side effects [422,417]. However, since the primary aim of the Chinese study was to assess phenobarbital efficacy, the investigators removed all individuals who were non-adherent to

phenobarbital treatment for three consecutive visits [423]. Removal of these non-adherent individuals may have led to underestimation of the true incidence of phenobarbital-related adverse events since adverse events have been repeatedly associated with decreased medication adherence [231,320-322]. Lastly, Zambian participants would have no reason to feel uncomfortable reporting phenobarbital-related side effects to our ECT interviewers as they do not hold positions of authority, official or symbolic. Interestingly, the mean total side effects score reported in this study was significantly lower than that reported in cohort of people with epilepsy in United States and United Kingdom taking AEDs that are traditionally better tolerated (37.3 vs. 22.57, $p<0.001$) [424]. This may reflect greater acceptance and potential underreporting of adverse effects in our cohort due to limited alternative AED regimens.

The findings in this study are limited by our small sample size as well as our inability to objectively verify medication adherence. Yet, they suggest a need for further investigation into reported AED side effects among people with epilepsy obtaining phenobarbital treatment in low-income settings as part of routine clinical care, especially because phenobarbital use may increase in this setting [425].

There is a general consensus that decreasing the epilepsy treatment gap is necessary in low-income settings [27,18]. To succeed, AEDs must be consistently accessible and patients must adhere to prescribed drugs. Adverse events and fear of adverse events are often common causes of decreased drug adherence [426], and accurate assessment of adverse events, both among individuals initiating an AED and among individuals on maintenance therapy, is essential for understanding a key driver of poor adherence and improving efforts to decrease the epilepsy treatment gap.

# CHAPTER 5:

# ADVERSE EVENTS ASSOCIATED WITH CONCURRENT TREATMENT WITH ANTIRETROVIRAL DRUGS AND AN ENZYME-INDUCING ANTIEPILEPTIC DRUG IN ZAMBIA


## Abstract

*Objective*

Concurrent treatment with combination antiretroviral therapy (cART) and an enzyme-inducing antiepileptic drug (EI-AED) in patients with comorbid HIV and seizure disorders may have long-term health implications by decreasing therapeutic efficacy and/or increase drug toxicity for one or both classes of medication. Despite the potential for significant drug-drug interactions, little is known about the effect of concurrent treatment on patient-reported adverse events and medication adherence. We aimed to determine the frequency and spectrum of patient-reported adverse events in individuals taking cART and an EI-AED in Zambia and whether adverse events were associated with decreased medication adherence.

*Methods*

We assessed patient-reported adverse events among three groups of patients: those initiating combined cART and an EI-AED (cART+EI-AED), those initiating cART only (cART-only), those taking neither cART nor an EI-AED (Untreated). Adverse events were assessed in two ways: first via spontaneous report, as they are often ascertained during routine clinic visits, and, second, via checklists. For patients in the cART+EI-AED and cART-only groups, adverse events were assessed prior to initiation and again two weeks after initiating treatment. For all

participants, the severity of adverse events ascertained via checklist were graded using pre-established definitions. $CD4^+$ T-cell count, HIV staging using the WHO clinical staging criteria, and liver function using alanine transferase (ALT) levels were also obtained for all participants. For participants in the cART+EI-AED and cART only groups, medication adherence was obtained during two-week follow up visits using self-report.

Participant demographics and clinical characteristics were compared between treatment groups using one-way ANOVA and $\chi^2$ tests, as appropriate. Frequency distributions were examined in relation to spontaneously reported adverse events and for medication adherence. Participants were deemed adherent if they had taken at least 90% of their medication as prescribed. Adverse events assessed via checklist were analyzed separately as continuous variables using Cochran-Mantel-Haenszel statistics. For participants in the cART+EI-AED and cART-only groups, Bowker's test of symmetry and paired t-tests were used to compare paired adverse events reported at baseline and two weeks after initiating treatment.

*Results*

One hundred and fourty-five (145) participants were interviewed to assess patient-reported adverse events (20 cART+EI-AED; 43 cART-only; 82 Untreated). Participants in the cART+EI-AED had a higher baseline mean $CD4^+$ T-cell count than participants in the cART-only and Untreated groups (p=0.003). More participants in our study reported adverse events when they were asked about symptoms via checklist than when asked to report adverse events spontaneously. A baseline, there were significant differences in reported headache (p=0.002), problems walking (p=0.015), general weakness (p=0.003), problems thinking (p=0.003), and

depression (p=0.017). Using paired t-tests, more participants in the cART+EI-AED group reported experiencing nausea or vomiting at follow up than at baseline (p=0.049). No change in adverse events reported at baseline and at two weeks was detected among individuals in the cART-only group. Medication adherence was greater than 90% in for most participants the cART+EI-AED and cART-only groups.

*Conclusions*

Patient initiating concurrent cART+EI-AED were generally more symptomatic than patients initiating only cART or patients taking neither drug despite having a higher baseline $CD4^+$ T-cell count. Concurrent treatment with cART+EI-AED was associated with increased nausea and vomiting. Baseline illness and treatment-related adverse events may decrease medication adherence among patient taking multiple medications and, as a result, patient-reported adverse events associated with concurrent treatment with cART+EI-AED warrant additional investigation.

## Introduction

Increased availability of combination antiretroviral therapy (cART) has dramatically altered the course of the HIV epidemic [9,427-431]. By decreasing the rate of HIV replication and restoring immune function, cART prolongs survival [252,432,433,6,434-443] and reduces the likelihood of HIV transmission to uninfected individuals [255,432,444,445]. However, sustained medication adherence is required for cART to be successful [446,447,260,261,448-452]. Research suggests that cART adherence is impacted by individual and community level factors, such as gender [453-456], age [457,453,458,455,459,460], social support [461,458,454,455,459,462,460,463], and socioeconomic status [461,464], as well as clinical factors like medication cost [465,149,466-469], treatment complexity [470,471,457,472,453,458,454,473,474], and adverse events [471,149,453,475,476,459,477-481]. While many of these factors have been well-studied, the relationship between adverse events and adherence merits additional attention.

Although short-term adverse events have been well-reported in the literature [256] and the WHO has established grading criteria for cART-associated adverse events [482], there is no uniform method for assessing and reporting adverse events for clinical research. As shown in Table 5.1, instruments designed to assess HIV-associated symptoms and cART side effects vary considerably. Many studies examining cART-related side effects do not report which side effects were assessed [477,270,483-486]. Unfortunately, studies relying on chart documentation of side effects [268] may underestimate cART-related adverse events as they are often underreported in routine clinical settings [297,296].

Underreporting of adverse events is problematic, especially for patients taking cART concurrently with medications for other comorbidities. Concurrent medication usage may result

**Table 5.1: Instruments to Assess Symptoms Related to cART and HIV Infection**

| **Instrument** | **Medical Outcomes Study (MOS) Health Survey – HIV [487]** | **Unnamed – based on Justice et al. [279]** | **Symptom Distress Model** [488,489] | **Health-Related Quality of Life-Symptom Index [490]** | **HIV Symptoms Index** [491,478] | **MOS 36-item Short-Form Health Survey (SF-36)** [492,493] | **Revised Sign and Symptom Check-list for HIV[494]** | **Total times assessed** |
|---|---|---|---|---|---|---|---|---|
| Item type: | 6-point LT | 4-point LT | 5-point LT | 5-point LT | 4-point LT | 5-point LT and dichotomous | 3-point LT | - |
| Country | France [495], Germany [495] India [496,497], Italy [498,495], Netherlands [495], Spain [499], Thailand [500] USA[487], [501], UK [495] | Switzerland [279], | Cameroon [502], Italy[503], USA [503,488,489] | USA[490] | Italy [478], USA [491] | France [504,505], South Africa [506]o, Venezuela[507], USA [493,508] | Puerto Rico [509], South Africa [510,511], USA [512,494,513] | |
| **Symptom** | | | | | | | | |
| Anxiety | | | x | | | x | x | 3 |
| Ataxia/ Unsteadiness | | | | | x | | | 1 |
| Blurred vision | | | | | | | x | 1 |
| Blood in spit/sputum | | | | | | | x | 1 |
| Body pain | x | | | | | | | 1 |
| Breast pain | | | | | | | x | 1 |
| Burning with urination | | | | | | | x | 1 |

LT: Likert-type responses

**Table 5.1 (cont'd)**

| **Instrument** | **Medical Outcomes Study (MOS) Health Survey – HIV [487]** | **Unnamed – based on Justice et al. [279]** | **Symptom Distress Model** [488,489] | **Health-Related Quality of Life-Symptom Index [490]** | **HIV Symptoms Index** [491,478] | **MOS 36-item Short-Form Health Survey (SF-36)** [492,493] | **Revised Sign and Symptom Check-list for HIV[494]** | **Total times assessed** |
|---|---|---|---|---|---|---|---|---|
| Changes in taste | | | | | | x | | 1 |
| Chest pain | | | | | | | x | 1 |
| Chills | | | | | | | x | 1 |
| Concentration | x | | | | | | x | 2 |
| Constipation | | | | | | x | x | 2 |
| Cough | | | x | | x | x | x | 4 |
| Day sweats | | | | | | | x | 1 |
| Depression | x | | x | | x | x | x | 5 |
| Diarrhea | | x | x | x | x | x | x | 6 |
| Disturbed sleep | | x | x | x | x | x | x | 6 |
| Dizziness | | | x | | | x | x | 3 |
| Dry mouth | | | | | | x | x | 2 |
| Easy bruising | | | | | | | x | 1 |
| Fear | | | | | | | x | 1 |
| Fever | | x | x | x | x | x | x | 5 |
| Flushing | | | | | | | x | 1 |
| Forgetfulness | x | | x | | | | | 2 |
| Gas/Bloating | | | | | | | x | 1 |
| Hair loss | | | x | | | x | | 2 |
| Headache | | x | x | | x | x | x | 5 |
| Heart racing | | | | | | | x | 1 |
| Hump on neck/ shoulders | | | | | | | x | 1 |
| Impotence | | | x | | | x | | 2 |

**Table 5.1 (cont'd)**

| **Instrument** | **Medical Outcomes Study (MOS) Health Survey – HIV [487]** | **Unnamed – based on Justice et al. [279]** | **Symptom Distress Model** [488,489] | **Health-Related Quality of Life-Symptom Index [490]** | **HIV Symptoms Index** [491,478] | **MOS 36-item Short-Form Health Survey (SF-36)** [492,493] | **Revised Sign and Symptom Check-list for HIV[494]** | **Total times assessed** |
|---|---|---|---|---|---|---|---|---|
| Inability to eat | | | x | | | | | 1 |
| Itchy Skin | | | | | | | x | 1 |
| Limited activities | x | | | | | | | 1 |
| Lipodystrophy | | | x | | | x | x | 3 |
| Loss of Appetite | | | x | | | x | x | 3 |
| Loss of strength | | | | | | x | | 1 |
| Memory problems | | | | x | x | x | x | 4 |
| Mood disorders | | x | | | | | | 1 |
| Mouth ulcers | | | | | | | x | 1 |
| Muscle pain | | x | x | x | | x | x | 5 |
| Nausea/Vomiting | | x | x | x | x | x | x | 6 |
| Nephrolithiasis | | x | | | | | | 1 |
| Nervousness | x | | | | | x | | 2 |
| Neurologic symptoms | | | | x | | x | | 2 |
| Night sweats | | | | | | x | x | 2 |
| Nipple discharge | | | | | | | x | 1 |
| Nose bleeds | | | | | | | x | 1 |
| Painful joints | | | | | | x | x | 2 |
| Painful swallowing | | | | | | | x | 1 |
| Paresthesia | | x | | | x | | x | 3 |
| Prominent veins | | | | | | | x | 1 |

**Table 5.1 (cont'd)**

| **Instrument** | **Medical Outcomes Study (MOS) Health Survey – HIV [487]** | **Unnamed – based on Justice et al. [279]** | **Symptom Distress Model** [488,489] | **Health-Related Quality of Life-Symptom Index [490]** | **HIV Symptoms Index** [491,478] | **MOS 36-item Short-Form Health Survey (SF-36)** [492,493] | **Revised Sign and Symptom Check-list for HIV[494]** | **Total times assessed** |
|---|---|---|---|---|---|---|---|---|
| Poor mental health | | | | x | | | | 1 |
| Rash | | x | x | | x | x | x | 5 |
| Rectal itching, bleeding or discharge | | | | | | | x | 1 |
| Seizures/tremors | | | | | | | x | 1 |
| Shortness of breath | | | | | | | x | 1 |
| Sore/bleeding gums | | | | | | | x | 1 |
| Sore throat | | | | | | x | | 1 |
| Sores or lumps on genitals | | | | | | | x | 1 |
| Swollen feet | | | | | | | x | 1 |
| Swollen glands | | | | | | | x | 1 |
| Thirst | | | | | | | x | 1 |
| Thrush | | | | | | | x | 1 |
| Tiredness/Fatigue | x | x | x | x | x | x | | 7 |
| Upset stomach | | | | | | x | x | 2 |
| Weakness | | | | | | | x | 1 |
| Weight loss | | | x | | | x | x | 3 |
| Wheezing | | | | | | x | x | 2 |

in drug interactions that decrease treatment efficacy while increasing patient-reported adverse events [514,515]. Although multiple review articles have discussed adverse events resulting from drug interactions between cART and unrelated medications [516-522], few researchers have examined adverse events in patients with comorbid conditions obtaining routine HIV care. Hasan et al. examined drug interactions in 325 patients, yet did not compare adverse events reported by individuals taking multiple medications to adverse events reported by individuals taking only cART [486]. Shah et al. found that individuals taking two or more medications for comorbid conditions were no more likely to discontinue cART due to toxicity than individuals taking fewer than two additional medical medications [523]. However, few participants were taking cART alone.

As HIV-positive individuals continue to live longer, more individuals on cART will require additional medications for comorbid medical conditions [524,515]. Antiepileptic drugs are often prescribed to HIV-positive individuals to prevent recurrent seizures and to manage peripheral neuropathy and psychiatric conditions like bipolar disorder [525]. As multiple cohorts have shown that more than 10% of HIV-positive individuals develop new-onset seizures [15,16], the potential overlap between cART and antiepileptic drugs is considerable [353]. In low-income settings, enzyme-inducing antiepileptic drugs (EI-AEDs), such as carbamazepine and phenobarbital, are usually the only anti-seizure medications available [526,358] and both have been associated with substantial side effects. Table 5.2 lists the adverse events assessed by multiple instruments used with patients taking AEDs.

Simultaneous treatment with an EI-AED and antiretroviral medications that are either non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs) may result in decreased effectiveness of both medications due to induction of Cytochrome P450 liver

**Table 5.2: Instruments to Assess Adverse Events Associated with AEDs**

| **Instrument** | **Liverpool Adverse Events Profile** [424,359,421,420, 527] | **Portland Neuro-toxicity Scale** [528] | **Parent Side Effect Scale** [418,42 2] | **Side Effect and Life Satisfaction Inventory (SEALS)** [529] | **A-B Neuropsych-ological Assessment Schedule** [530] | **Toxicity of Antiepileptic Drugs on Well-Defined Types of Seizures** [531] | **Assessing SIDe effects in AED treatment (SIDAED) [419]** | **Total times assessed** |
|---|---|---|---|---|---|---|---|---|
| Question type: | 3-point LT | 9-point LT | 4-point LT | 4-point LT | 4-point LT | Dichotomous | 4-point LT | |
| Country | Australia [421], Brazil [532], China [533], Croatia, Finland, France, Norway [534], Italy [535], Mexico [359], Spain [536], UK [424,527], USA [424] | USA [528] | Nether-lands [418], Spain [422] | UK [314] | Netherlands [530] | USA [531] | Netherland s [419] | |
| **Symptom** | | | | | | | | |
| Acne | | | | | | x | | 1 |
| Aggression | x | | x | x | x | x | | 5 |
| Alertness | | x | | | | | | 1 |
| Anxiety | x | | | x | | x | | 3 |
| Ataxia | x | x | x | | x | x | x | 6 |
| Behavioral disturbance | | | x | | | | | 1 |
| Blurred vision | x | x | x | | | x | x | 5 |
| Concentration | x | x | x | x | x | | x | 6 |
| Confusion | | | | | | x | | 1 |

LT: Likert-type responses

**Table 5.2 (cont'd)**

| **Instrument** | **Liverpool Adverse Events Profile** [424,359,421,420,527] | **Portland Neurotoxicity Scale** [528] | **Parent Side Effect Scale** [418,422] | **Side Effect and Life Satisfaction Inventory (SEALS)** [529] | **A-B Neuropsych-ological Assessment Schedule** [530] | **Toxicity of Antiepileptic Drugs on Well-Defined Types of Seizures** [531] | **Assessing SIDe effects in AED treatment (SIDAED) [419]** | **Total times assessed** |
|---|---|---|---|---|---|---|---|---|
| Constipation | | | x | | | | x | 2 |
| Coordination | | x | x | | x | | | 3 |
| Depression | x | | x | | x | x | x | 5 |
| Diarrhea | | | x | | | | x | 2 |
| Disturbed sleep | x | | | | | | | 1 |
| Dizziness | x | | x | | | x | x | 4 |
| Excess saliva | | | | | | | x | 1 |
| Forgetfulness | | x | | x | x | | x | 4 |
| Gastrointest-inal Distress | | | | | | x | | 1 |
| Hair loss | x | | | | | | | 1 |
| Headache | x | | x | | | x | x | 4 |
| Hirsutism | | | | | | x | x | 2 |
| Hyperactivity | | | x | | x | | | 2 |
| Impotence | | | | | | x | x | 2 |
| Insomnia | | | | | | | x | 1 |
| Irritability | | | | | x | | | 1 |
| Loss of Appetite | | | x | | | | x | 2 |
| Loss of Interest | | x | | | x | | | 2 |

**Table 5.2 (cont'd)**

| **Instrument** | **Liverpool Adverse Events Profile**[424,359,421,420,527] | **Portland Neurotoxicity Scale**[528] | **Parent Side Effect Scale**[418,422] | **Side Effect and Life Satisfaction Inventory (SEALS)**[529] | **A-B Neuropsych-ological Assessment Schedule**[530] | **Toxicity of Antiepileptic Drugs on Well-Defined Types of Seizures**[531] | **Assessing SIDe effects in AED treatment (SIDAED)[419]** | **Total times assessed** |
|---|---|---|---|---|---|---|---|---|
| Memory loss | x | x | | | x | | | 3 |
| Mental slowness | | | x | x | x | | | 3 |
| Mood swings | | x | | | | | | 1 |
| Mouth/gums | x | | | | | x | x | 3 |
| Nausea/ Vomiting | | | | | x | | x | 2 |
| Nystagmus | | | | | | x | | 1 |
| Physical slowness | | | | | x | | x | 2 |
| Poor school performance | | | x | | | | | 1 |
| Rash | x | | | | | x | x | 3 |
| Restlessness | x | | | | | | | 1 |
| Sedation | x | x | x | x | | x | x | 6 |
| Sickness | | | x | | | | | 1 |
| Speech difficulties | | x | x | | x | x | x | 5 |
| Fatigue | x | x | x | x | x | | x | 6 |
| Tremor | x | x | x | | | x | x | 5 |
| Upset stomach | x | | | | | | x | 2 |
| Weight change | x | | | | | | x | 1 |

enzymes (CYP450). This interaction may manifest as increased HIV replication, recurrent seizures, and altered severity of patient-reported adverse events [353]. Although pharmacokinetic and clinical studies suggests that co-treatment with cART and an EI-AED result in loss of seizure control and the development of cART treatemtn failure for HIV-positive individuals [353,352,348,356,355], there is limited data regarding patient-reported adverse events or adverse outcomes related to co-usage among patients taking both drugs simultaneously [537].

We examined patient-reported adverse events among HIV-positive individuals taking an EI-AED with cART as part of routine clinical care in Lusaka, Zambia. Adverse events reported by individuals initiating an EI-AED and cART were compared to the adverse events reported by HIV-positive individuals initiating cART only and HIV-positive individuals taking neither cART nor an EI-AED. For individuals initiating a treatment regimen, change in severity of adverse events and medication adherence were assessed two weeks after initiation.

**Methods**

Between January 18, 2013 and February 13 2014, participants were recruited from the Cohort Study of HIV-Associated Seizures and Epilepsy (CHASE) and the University of Zambia's University Teaching Hospital (UTH) Adult Infectious Disease Centre of Excellence (AIDC) in Lusaka, Zambia. CHASE is a United States National Institutes of Health (NIH)-funded study examining the etiology and long-term health outcomes of HIV-positive individuals experiencing new-onset, unprovoked seizure. All participants were followed through the AIDC. The AIDC treats patients who were either diagnosed as HIV-positive while admitted to the UTH or who were referred in from a community HIV clinic with complications after initiating cART.

All CHASE participants meeting the eligibility criteria were included in this study, whereas only AIDC patients whose clinic file numbers ended in 0, 4, 5, or 9 were assessed for study inclusion.

Eligibility criteria included: between the ages of 18 and 60 years; medical records documentation of HIV-positive; not pregnant, based on female patient report; a score of 17/24 or greater on the Zambian Mini-Mental Status exam indicating mild or no cognitive impairment [389]; and fit into one of the four eligible treatment groups described below. Medical records were used to assess patient age and HIV status before patients were approached to determine whether they met the remaining eligibility criteria. Patients taking fluconazole to prevent recurrent Cryptococcal meningitis or rifampin-based Anti-Tuberculosis Treatment (ATT) were eligible for study inclusion only if they had been taking fluconazole or ATT for more than one month as both drugs have been shown to affect CYP450 activity [538,539].

To investigate the adverse events associated with cART and EI-AED co-usage, eligible study participants were divided into three groups based on medication status. The first treatment group included individuals initiating co-treatment with cART and an EI-AED (either carbamazepine or phenobarbital). The cART+EI-AED group included: individuals taking an EI-AED for a pre-existing seizure disorder and initiating cART due to a $CD4^+$ T-cell count less than 350 cells/$mm^3$; individuals taking cART with a history of untreated seizures who were initiating an EI-AED; and individuals initiating both an EI-AED due to a history of untreated seizures and initiating cART due to a $CD4^+$ T-cell count less than 350 cells/$mm^3$. The second treatment group included individuals who had not experienced a seizure and were initiating cART for the first time due to $CD4^+$ T-cell count less than 350 cells/$mm^3$. Per clinic protocol, individuals in the cART-only group were also taking trimethoprim/sulfamethoxazole (TMP/SMX) for at least

two weeks as prophylaxis against *Pneumocystis carinii* pneumonia, unless they had a $CD4^+$ T-cell count greater than 200 cells/$mm^3$ or were allergic. It was anticipated that participants in the cART+EI-AED group would largely be prescribed first-line cART which includes an NNRTI. However, if a cART+EI-AED participant was taking a second-line cART regimen that included a PI instead of an NNRTI, two individuals initiating PI-based cART were also recruited for the cART-only group. The third treatment group included individuals who had not experienced seizure and had not yet initiated cART. Individuals in this Untreated group were either attending the clinic for the first time and were undergoing assessment for cART eligibility or had undergone eligibility assessment and were participating in pre-treatment adherence counseling. Per clinic protocol, individuals undergoing adherence counseling were taking TMP/SMX. A fourth treatment group of HIV-positive individuals initiating only an EI-AED had been planned. However, as most individuals in this treatment group were also eligible to initiate cART due to a $CD4^+$ T-count below 350 cells/$mm^3$ [540], recruitment for this group was halted on November 25, 2013.

A trained Zambian nurse read the study consent form aloud and discussed it with eligible patients in a private room before obtaining written, informed consent in the language of their choice (Nyanja, Bemba, or English). All participants were interviewed before or after being seen by a health care provider at the AIDC. Participants in the Untreated group were interviewed once, whereas participants in the cART+EI-AED and cART-only groups were interviewed twice - before initiating their treatment and again two weeks later to assess changes in patient-reported adverse events. Medication adherence was also assessed at the two week follow up visit for participants in the cART+EI-AED and cART-only groups. An interval of two weeks between

interviews was selected to decrease loss to follow up. All patients starting medications at the AIDC attend a two week follow up appointment; scheduling of subsequent visits varies considerably. At the end of each interview, participants were reimbursed 20 Kwacha (~4 USD) to cover their transportation to the clinic.

The University of Zambia's Biomedical Research Ethics Committee (UNZA BREC) and Michigan State University's Biomedical Institutional Review Board (MSU BIRB) provided ethical approval of this study prior to initiation.

*Instruments*

Study participant demographics, reported adverse events, and simultaneous medication usage (other than cART and EI-AEDs) were collected via structured interview. HIV stage at the time of interview, using the WHO clinical staging criteria [255], $CD4^+$ T-cell count, and liver function using alanine transferase (ALT) level were abstracted from participants' medical records. Testing for Hepatitis B and C were not performed because Hepatitis B testing availability varied considerably during the study period and Hepatitis C testing was unavailable.

Adverse events were assessed in two ways. First, participants were asked to list any general medical or neurological problems they experienced in the past two weeks. This was done as this is the approach traditionally used to assess adverse events in routine clinical settings. Second, participants were asked about the occurrence of sixteen specific adverse events in the previous two weeks. We selected these adverse events for assessment by comparing existing instruments designed to assess cART and AED adverse events to the side effects frequently reported for NNRTIs, PIs, and EI-AEDs. Participants were asked whether they had experienced the adverse event in the previous two weeks and, if so, to describe it. Using pre-established

definitions (Appendix 1), responses were graded as mild, moderate, and severe based on limitations imposed by the adverse event and treatment sought

To assess medication adherence, participants in the cART+EI-AED and cART-only groups were asked about any problems taking their medications; the number of doses missed during the previous three days; and to rank the number of pills they had taken on a visual analog scale. This approach is used routinely to assess cART adherence at the AIDC and has been used previously as part of research studies in this setting [174]. Pill counts were abandoned as most participants did not bring their medication to their follow up visit. Participants were deemed adherent to their medication if they reported taking at least 90% of their medication as prescribed.

*Statistical Analysis*

Participant responses were recorded on paper copies of the survey instrument then entered into Microsoft Access and verified for accuracy. We used one-way ANOVA and $\chi^2$ tests, as appropriate, to compare participant demographics and clinical characteristics between the three treatment groups. Simple frequencies were performed for adverse events that were spontaneously reported by participants, both at baseline and at follow up, and medication adherence for individuals in the cART+EI-AED and cART-only groups.

The 16 adverse events that were assessed via checklist were analyzed independently of one another. Categorical responses for the severity of each adverse event were graded as follows for continuous analyses: None=0, Mild=1, Moderate=2, and Severe=3. Adverse events reported at baseline by all treatment groups were ordered according to severity. We then used Cochran-Mantel-Haenszel statistics to compare the severity of symptoms across treatment groups.

For participants in the cART+EI-AED and cART-only groups, adverse events reported at baseline and two weeks after initiating treatment were paired to assess change in symptom severity using Bowker's test of symmetry and paired t-tests. Bowker's test of symmetry is a generalization of McNemar's test for square tables larger than 2x2 and assesses the agreement between categorical proportions reported at baseline and at two weeks. Paired t-tests examine whether there is a paired difference in means between adverse events reported at baseline and at two weeks.

All statistical analyses were performed in SAS (version 9.4, SAS Institute, Inc., Cary). A p-value of less than 0.05 was considered significant.

**Results**

One hundred and forty-five participants were interviewed to assess patient-reported adverse events (20 cART+EI-AED; 43 cART-only; 82 Untreated). Twenty-five participants were recruited from the CHASE study; the remaining 120 participants were recruited while obtaining routine outpatient care at the AIDC. In addition to those interviewed, 30 eligible patients did not consent to participate in the study – twelve left the clinic before being interviewed; four were UTH staff and cited privacy concerns; two said they were too busy to participate; and twelve provided no justification. There were no significant differences in gender or age between patients that consented and patients that declined study participation (gender: 54% vs. 52%, p=0.84; age 37yrs vs. 40yrs p=0.18).

Table 5.3 shows participants' baseline demographic and clinical information by treatment group. Participants in the cART+EI-AED group had a higher mean $CD4^+$ T-cell count than participants in the cART-only and Untreated groups (p=0.028). Six participants (30%) in the

cART+EI-AED group had a $CD4^+$ T-cell count above 350 cells/$mm^3$. Participants in the cART-only group more likely to be taking TMP/SMX than participants in the cART+EI-AED or Untreated group (p=0.004). There were no other significant differences between groups.

**Table 5.3: Demographic and Clinical Characteristics of Study Participants**

| | **cART+EI-AED (n=20)** | **cART-only (n=43)** | **Untreated (n=82)** | **P-value** |
|---|---|---|---|---|
| Female gender (%) | 9 (45%) | 23 (53%) | 44 (54%) | 0.798 |
| Age, mean (SD) | 34.7 (9.4) | 37.6 (8.6) | 37.7 (9.8) | 0.421 |
| $CD4^+$ count, (cells/$mm^3$) mean (SD) | 297 (259) | 158 (118) | 212 (200) | **0.028** |
| CD4>350 cells/$mm^3$ (%) | 6 (30%) | 1 (2%) | 16 (20%) | |
| ALT, mean (SD) | 40.7 (60.8) | 35.9 (53.6) | 35.2 (37.7) | 0.890 |
| Missing | 0 | 2 | 1 | |
| WHO Stage | | | | |
| I | 6 (30%) | 15 (35%) | 22 (28%) | 0.107 |
| II | 1 (5%) | 0 (0%) | 9 (12%) | |
| III | 5 (25%) | 20 (47%) | 29 (37%) | |
| IV | 8 (40%) | 8 (40% | 18 (23%) | |
| Missing | 0 | 0 | 2 | |
| Taking other drugs | | | | |
| TMP/SMX | 11 (55%) | 35 (81%) | 42 (51%) | **0.004** |
| ATT | 6 (30%) | 12 (29%) | 23 (28%) | 0.985 |
| Fluconazole | 0 (0%) | 3 (7%) | 4 (5%) | 0.559 |

Of the 20 participants in the cART+EI-AED group, ten participants were already taking cART and initiating an EI-AED; nine participants were already taking an EI-AED and initiating cART; and one participant was initiating both drugs simultaneously. All of the participants initiating an EI-AED had experienced a seizure in the previous 24 hours. For EI-AEDs, eighteen participants were prescribed carbamazepine 200mg twice daily (BD) for generalized tonic-clonic seizures. One participant was taking carbamazepine 200mg once daily (OD) for post-herpetic neuralgia and one participant was prescribed phenobarbital 90mg OD for non-convulsive status

epilepticus. Fifteen participants in the cART+EI-AED group were taking fixed-dose tenofovir (TDF), emtricitabine (FTC), efavirenz (EFV 600mg) OD for cART. Of the remaining five participants, one was taking an efavirenz-based regimen (600mg OD), two were taking a nevirapine-based regimen (200mg BD) and one was taking lopinavir/ritonavir (400/100mg BD). Of the 43 participants in the cART-only group, 39 were initiating TDF/FTC/EFV; one was initiating an efavirenz-based regimen; one was initiating a nevirapine-based regimen; and two additional participants were initiating a lopinavir/ritonavir regimen.

At baseline, 17 different medical and neurological problems were elicited spontaneously from all 145 participants. As shown in Table 5.4, headache was the most common complaint. Eighty-three participants (57%) volunteered no medical or neurological problems.

**Table 5.4: Adverse Events Reported Spontaneously at Baseline by Study Participants**

| Medical Problem | cART+EI-AED (n=20) | cART-only (n=43) | Untreated (n=82) |
|---|---|---|---|
| Blurry vision | 1 | | 1 |
| Constipation | | 1 | |
| Cough | | 3 | 2 |
| Dizziness | | | 1 |
| Enlarged lymph nodes | | | 2 |
| Fever | | 1 | |
| General weakness | | 1 | 1 |
| Hallucinations | | 1 | |
| Headache | 5 | 9 | 27 |
| Herpes Zoster | 1 | | 1 |
| Kaposi Sarcoma | | 1 | |
| Localized pain | 2 | 3 | 2 |
| Nightmares | 1 | | |
| Oral Thrush | | | 2 |
| Peripheral neuropathy | | 1 | 2 |
| Tonsillitis | | | 1 |
| Upset stomach | 1 | | 2 |

Table 5.5 shows the baseline severity for the 16 patient-reported adverse events queried for all of the treatment groups. Thirty participants (21%) reported experiencing none of the

**Table 5.5: Adverse Events Reported By Checklist at Baseline**

| Symptom | Group | None | Mild | Moderate | Severe | P-value |
|---|---|---|---|---|---|---|
| Rash | Start cART+EI-AED | 18 (90%) | 2 (10%) | 0 (0%) | 0 (0%) | 0.921 |
| | Start cART-only | 38 (88%) | 5 (12%) | 0 (0%) | 0 (0%) | |
| | Untreated | 73 (89%) | 7 (9%) | 2 (2%) | 0 (0%) | |
| Diarrhea | Start cART+EI-AED | 17 (85%) | 3 (15%) | 0 (0%) | 0 (0%) | 0.869 |
| | Start cART-only | 36 (84%) | 6 (14%) | 1 (2%) | 0 (0%) | |
| | Untreated | 67 (82%) | 13 (16%) | 2 (2%) | 0 (0%) | |
| Nausea or Vomiting | Start cART+EI-AED | 19 (95%) | 1 (5%) | 0 (0%) | 0 (0%) | 0.163 |
| | Start cART-only | 39 (91%) | 4 (9%) | 0 (0%) | 0 (0%) | |
| | Untreated | 67 (54%) | 14 (17%) | 1 (1%) | 0 (0%) | |
| Abdomin-al pain | Start cART+EI-AED | 16 (80%) | 3 (15%) | 1 (5%) | 0 (0%) | 0.822 |
| | Start cART-only | 34 (79%) | 8 (19%) | 1 (2%) | 0 (0%) | |
| | Untreated | 62 (76%) | 16 (19%) | 4 (5%) | 0 (0%) | |
| Dizziness | Start cART+EI-AED | 14 (70%) | 5 (25%) | 1 (5%) | 0 (0%) | 0.489 |
| | Start cART-only | 33 (77%) | 9 (21%) | 1 (2%) | 0 (0%) | |
| | Untreated | 65 (79%) | 14 (17%) | 3 (4%) | 0 (0%) | |
| Sleepiness | Start cART+EI-AED | 14 (70%) | 5 (25%) | 1 (5%) | 0 (0%) | 0.581 |
| | Start cART-only | 35 (81%) | 7 (16%) | 1 (2%) | 0 (0%) | |
| | Untreated | 63 (77%0 | 14 (17%) | 5 (6%) | 0 (0%) | |
| Headache | Start cART+EI-AED | 6 (30%) | 10 (50%) | 3 (15%) | 1 (5%) | **0.002** |
| | Start cART-only | 29 (67%) | 13 (30%) | 1 (2%) | 0 (0%) | |
| | Untreated | 49 (60%) | 28 (34%) | 5 (6%) | 0 (0%) | |
| Problems walking | Start cART+EI-AED | 15 (75%) | 3 (15%) | 1 (5%) | 1 (5%) | **0.015** |
| | Start cART-only | 41 (95%) | 2 (5%) | 0 (0%) | 0 (0%) | |
| | Untreated | 70 (85%) | 11 (13%) | 1 (1%) | 0 (0%) | |
| Vision problems | Start cART+EI-AED | 19 (95%) | 1 (5%) | 0 (0%) | 0 (0%) | 0.648 |
| | Start cART-only | 42 (98%) | 1 (2%) | 0 (0%) | 0 (0%) | |
| | Untreated | 77 (94%) | 5 (6%) | 0 (0%) | 0 (0%) | |
| Weakness in arms or legs | Start cART+EI-AED | 13 (65%) | 5 (25%) | 1 (5%) | 1 (5%) | 0.083 |
| | Start cART-only | 34 (79%) | 8 (19%) | 1 (2%) | 0 (0%) | |
| | Untreated | 64 (78%) | 18 (22%) | 0 (0%) | 0 (0%) | |
| Numbness Tingling | Start cART+EI-AED | 15 (75%) | 5 (25%) | 0 (0%) | 0 (0%) | 0.128 |
| | Start cART-only | 41 (96%) | 1 (2%) | 1 (2%) | 0 (0%) | |
| | Untreated | 66 (80%) | 13 (16%) | 2 (2%) | 0 (0%) | |
| General weakness | Start cART+EI-AED | 9 (45%) | 10 (50%) | 0 (0%) | 1 (5%) | **0.003** |
| | Start cART-only | 36 (83%) | 5 (12%) | 2 (5%) | 0 (0%) | |
| | Untreated | 67 (82%) | 13 (16%) | 2 (2%) | 0 (0%) | |

**Table 5.5 (cont'd)**

| Symptom | Group | None | Mild | Moderate | Severe | P-value |
|---|---|---|---|---|---|---|
| Problems Thinking | Start cART+EI-AED | 13 (65%) | 4 (20%) | 3 (15%) | 0 (0%) | **0.003** |
| | Start cART-only | 40 (93%) | 2 (5%) | 1 (2%) | 0 (0%) | |
| | Untreated | 74 (90%) | 6 (7%) | 2 (2%) | 0 (0%) | |
| Memory Problems | Start cART+EI-AED | 15 (75%) | 5 (25%) | 0 (0%) | 0 (0%) | 0.796 |
| | Start cART-only | 36 (84%) | 6 (14%) | 1 (2%) | 0 (0%) | |
| | Untreated | 65 (79%) | 14 (17%) | 3 (4%) | 0 (0%) | |
| Irritability | Start cART+EI-AED | 13 (65%) | 3 (15%) | 4 (20%) | 0 (0%) | 0.053 |
| | Start cART-only | 35 (81%) | 8 (19%) | 0 (0%) | 0 (0%) | |
| | Untreated | 61 (74%) | 18 (22%) | 3 (4%) | 0 (0%) | |
| Depression | Start cART+EI-AED | 13 (65%) | 4 (20%) | 3 (15%) | 0 (0%) | **0.017** |
| | Start cART-only | 35 (81%) | 8 (19%) | 0 (0%) | 0 (0%) | |
| | Untreated | 73 (89%) | 6 (7%) | 3 (4%) | 0 (0%) | |

adverse events (1 cART+EI-AED, 13 cART-only, 16 Untreated). Headache was the most commonly endorsed adverse event by all participants (61/145, 42%) followed by irritability (36/145, 25%). Overall, participants in the cART+EI-AED group were more symptomatic at baseline than participants in the other two treatment groups. There were significant differences in the severity of reported headache (p=0.002), problems walking (p=0.015), general weakness (p=0.003), problems thinking (p=0.0-03), and depression (p=0.017).

All participants in the cART+EI-AED and cART-only groups were interviewed two weeks following the start of their medications. During the two weeks after initiating treatment, medication adherence was high for both groups. Few participants said they had problems with their medication. Three people said that the pills were too large to swallow, and two said that they forgot to take the medications. In the three days prior to interview, one person in the cART+EI-AED group missed two doses of antiretroviral drugs while one person in the cART-only group missed one dose. Among individuals in the cART+EI-AED group, EI-AED

adherence was also high. Only one person had poor adherence; she forgot to take her carbamazepine for two days, though she remembered to take her cART.

Table 5.6 lists volunteered medical problems by participants in the cART+EI-AED and cART-only groups at two weeks follow up. Thirty-eight participants (60%) had no medical complaints. Two participants in the cART+EI-AED group who had started carbamazepine 200mg BD at their initial visit experienced generalized tonic-clonic seizures between visits.

**Table 5.6: Adverse Events Reported Spontaneously at Follow Up**

| Medical Problem | cART+EI-AED (n=20) | cART-only (n=43) |
|---|---|---|
| Constipation | 1 | |
| Diarrhea | | 1 |
| Dizziness | | 3 |
| Fever | 1 | |
| General weakness | 3 | 1 |
| Headache | 5 | 8 |
| Localized pain | 2 | 3 |
| Nausea/vomiting | 2 | 1 |
| Peripheral neuropathy | 2 | |
| Rash | | 1 |
| Sleepiness | 1 | 1 |
| Stammering | 1 | |
| Tremor | 1 | |
| Upset Stomach | | 1 |

Table 5.7 depicts the marginal counts for the change in patient-reported adverse events between initiating treatment and two weeks later for both the cART+EI-AED group and cART-only groups. We do not display the joint distribution for the change in adverse events in Table 5.7. Three participants in the cART+EI-AED group (15%) endorsed experiencing none of the queried adverse events compared to 10 participants (23%) in the cART-only group. No differences were detected in categorical proportions using Bowker's test of symmetry for any of the adverse events for either the cART+EI-AED or cART-only groups. Using paired t-tests,

**Table 5.7: Change in Adverse Events for Participants in the cART+EI-AED and cART-only groups**

| Adverse Event | Group | None | Mild | Moderate | Severe | Bowker's Test P-value | Paired T-test P-value |
|---|---|---|---|---|---|---|---|
| Rash | Starting cART+EI-AED | 18 (90%) | 2 (10%) | 0 (0%) | 0 (0%) | 0.392 | 1.0 |
| | cART+EI-AED Follow up | 19 (95%) | 1 (5%) | 0 (0%) | 0 (0%) | | |
| | Starting cART | 38 (88%) | 5 (12%) | 0 (0%) | 0 (0%) | 0.753 | 0.743 |
| | cART follow up | 38 (88%) | 4 (10%) | 1 (2%) | 0 (0%) | | |
| Diarrhea | Starting cART+EI-AED | 17 (85%) | 3 (15%) | 0 (0%) | 0 (0%) | 0.564 | 0.577 |
| | cART+EI-AED Follow up | 18 (90%) | 2 (10%) | 0 (0%) | 0 (0%) | | |
| | Starting cART | 36 (84%) | 6 (14%) | 1 (2%) | 0 (0%) | 0.543 | 1.0 |
| | cART follow up | 36 (84%) | 6 (14%) | 1 (2%) | 0 (0%) | | |
| Nausea or Vomiting | Starting cART+EI-AED | 19 (95%) | 1 (5%) | 0 (0%) | 0 (0%) | 0.284 | **0.049** |
| | cART+EI-AED Follow up | 14 (70%) | 4 (20%) | 2 (10%) | 0 (0%) | | |
| | Starting cART | 39 (91%) | 4 (9%) | 0 (0%) | 0 (0%) | 0.446 | 0.133 |
| | cART follow up | 36 (83%) | 5 (12%) | 2 (5%) | 0 (0%) | | |
| Abdominal pain | Starting cART+EI-AED | 16 (80%) | 3 (15%) | 1 (5%) | 0 (0%) | 0.978 | 0.789 |
| | cART+EI-AED Follow up | 15 (75%) | 4 (20%) | 1 (5%) | 0 (0%) | | |
| | Starting cART | 34 (79%) | 8 (19%) | 1 (2%) | 0 (0%) | 0.954 | 0.660 |
| | cART follow up | 36 (84%) | 6 (14%) | 1 (2%) | 0 (0%) | | |
| Dizziness | Starting cART+EI-AED | 14 (70%) | 5 (25%) | 1 (5%) | 0 (0%) | 0.570 | 0.505 |
| | cART+EI-AED Follow up | 11 (55%) | 8 (40%) | 0 (0%) | 1 (5%) | | |
| | Starting cART | 33 (77%) | 9 (21%) | 1 (2%) | 0 (0%) | 0.522 | 0.519 |
| | cART follow up | 30 (70%) | 12 (28%) | 1 (2%) | 0 (0%) | | |
| Sleepiness | Starting cART+EI-AED | 14 (70%) | 5 (25%) | 1 (5%) | 0 (0%) | 0.991 | 0.815 |
| | cART+EI-AED Follow up | 15 (75%) | 4 (20%) | 1 (5%) | 0 (0%) | | |
| | Starting cART | 35 (81%) | 7 (16%) | 1 (2%) | 0 (0%) | 0.230 | 0.057 |
| | cART follow up | 40 (93%) | 3 (7%) | 0 (0%) | 0 (0%) | | |

**Table 5.7 (cont'd)**

| Adverse Event | Group | None | Mild | Moderate | Severe | Bowker's Test P-value | Paired T-test P-value |
|---|---|---|---|---|---|---|---|
| Headache | Starting cART+EI-AED | 6 (30%) | 10 (50%) | 3 (15%) | 1 (5%) | 0.277 | **0.007** |
| | cART+EI-AED Follow up | 14 (70%) | 5 (25%) | 1 (5%) | 0 (0%) | | |
| | Starting cART | 29 (68%) | 13 (30%) | 1 (2%) | 0 (0%) | 0.912 | 0.555 |
| | cART follow up | 32 (74%) | 10 (23%) | 1 (2%) | 0 (0%) | | |
| Problems walking | Starting cART+EI-AED | 15 (75%) | 3 (15%) | 1 (5%) | 1 (5%) | 0.999 | 0.789 |
| | cART+EI-AED Follow up | 16 (80%) | 2 (10%) | 1 (5%) | 1 (5%) | | |
| | Starting cART | 41 (95%) | 2 (5%) | 0 (0%) | 0 (0%) | 0.655 | 0.660 |
| | cART follow up | 40 (93%) | 3 (7%) | 0 (0%) | 0 (0%) | | |
| Vision problems | Starting cART+EI-AED | 19 (95%) | 1 (5%) | 0 (0%) | 0 (0%) | 0.564 | 0.577 |
| | cART+EI-AED Follow up | 18 (90%) | 2 (10%) | 0 (0%) | 0 (0%) | | |
| | Starting cART | 42 (98%) | 1 (2%) | 0 (0%) | 0 (0%) | 0.564 | 0.569 |
| | cART follow up | 41 (95%) | 2 (5%) | 0 (0%) | 0 (0%) | | |
| Weakness in arms or legs | Starting cART+EI-AED | 13 (65%) | 5 (25%) | 1 (5%) | 1 (5%) | 0.587 | 1.0 |
| | cART+EI-AED Follow up | 12 (60%) | 6 (30%) | 2 (10%) | 0 (0%) | | |
| | Starting cART | 34 (79%) | 8 (19%) | 1 (2%) | 0 (0%) | 0.352 | 0.083 |
| | cART follow up | 39 (91%) | 4 (9%) | 0 (0%) | 0 (0%) | | |
| Numbness or Tingling | Starting cART+EI-AED | 13 (65%) | 5 (25%) | 1 (5%) | 1 (5%) | 0.103 | 0.104 |
| | cART+EI-AED Follow up | 19 (95%) | 1 (5%) | 0 (0%) | 0 (0%) | | |
| | Starting cART | 34 (79%) | 8 (19%) | 1 (2%) | 0 (0%) | 0.572 | 0.660 |
| | cART follow up | 39 (91%) | 4 (9%) | 0 (0%) | 0 (0%) | | |
| General Weakness | Starting cART+EI-AED | 9 (45%) | 10 (50%) | 0 (0%) | 1 (5%) | 0.062 | 0.204 |
| | cART+EI-AED Follow up | 16 (80%) | 0 (0%) | 4 (20%) | 0 (0%) | | |
| | Starting cART | 36 (83%) | 5 (12%) | 2 (5%) | 0 (0%) | 0.572 | 0.323 |
| | cART follow up | 37 (86%) | 6 (14%) | 0 (0%) | 0 (0%) | | |

**Table 5.7 (cont'd)**

| Adverse Event | Group | None | Mild | Moderate | Severe | Bowker's Test P-value | Paired T-test P-value |
|---|---|---|---|---|---|---|---|
| Problems Thinking | Starting cART+EI-AED | 13 (65%) | 4 (20%) | 3 (15%) | 0 (0%) | 0.572 | 0.572 |
| | cART+EI-AED Follow up | 15 (75%) | 3 (15%) | 2 (10%) | 0 (0%) | | |
| | Starting cART | 40 (93%) | 2 (5%) | 1 (2%) | 0 (0%) | 0.954 | 0.277 |
| | cART follow up | 41 (95%) | 1 (2%) | 1 (2%) | 0 (0%) | | |
| Memory Problems | Starting cART+EI-AED | 15 (75%) | 5 (25%) | 0 (0%) | 0 (0%) | 0.753 | 0.330 |
| | cART+EI-AED Follow up | 13 (65%) | 6 (30%) | 1 (5%) | 0 (0%) | | |
| | Starting cART | 36 (84%) | 6 (14%) | 1 (2%) | 0 (0%) | 0.733 | 0.445 |
| | cART follow up | 39 (91%) | 3 (7%) | 1 (2%) | 0 (0%) | | |
| Irritability | Starting cART+EI-AED | 13 (65%) | 3 (15%) | 4 (20%) | 0 (0%) | 0.675 | 0.649 |
| | cART+EI-AED Follow up | 13 (65%) | 5 (25%) | 2 (10%) | 0 (0%) | | |
| | Starting cART | 35 (81%) | 8 (19%) | 0 (0%) | 0 (0%) | 0.706 | 0.710 |
| | cART follow up | 36 (84%) | 7 (15%) | 0 (0%) | 0 (0%) | | |
| Depression | Starting cART+EI-AED | 13 (65%) | 4 (20%) | 3 (15%) | 0 (0%) | 0.954 | 0.666 |
| | cART+EI-AED Follow up | 12 (60%) | 4 (20%) | 4 (20%) | 0 (0%) | | |
| | Starting cART | 35 (81%) | 8 (19%) | 0 (0%) | 0 (0%) | 0.134 | 0.799 |
| | cART follow up | 38 (88%) | 3 (7%) | 2 (5%) | 0 (0%) | | |

more participants in the cART+EI-AED group reported experiencing nausea or vomiting at follow up than at baseline (p=0.049). In addition, fewer participants in the cART+EI-AED group reported headaches at follow up than at baseline (p=0.007). However, a *post hoc* analyses attributed this change to the presence of post-ictal headache among cART+EI-AED participants. Among individuals experiencing a seizure in the 12 hours prior to the baseline interview, headache severity decreased between interviews (p=0.009). There was no change among individuals who did not experience a seizure prior to their baseline interview (p=0.343). There were no significant differences between adverse events reported at baseline and at two weeks among individuals in the cART-only group using paired t-tests.

**Discussion**

Pharmacokinetic and clinical data suggest that combined treatment with cART and an EI-AED could result in decreased treatment efficacy. However, there are limited data regarding patient-reported adverse events resulting from this CYP450 drug interaction. This is one of the first studies to examine patient-reported adverse events among individuals taking cART with an EI-AED. Two weeks after initiating treatment, individuals taking cART and an EI-AED reported increased nausea and vomiting. No changes in patient-reported adverse events were detected among individuals initiating cART-only.

Previous research suggests that patients experiencing adverse events while taking cART frequently assign causality to either cART or HIV infection [541,493,542]. Gastrointestinal symptoms, such as nausea and vomiting, are frequently attributed to medication and, as a result, have been independently associated with decreased cART adherence [541,542]. Causal attribution of adverse events was not assessed in our cohort. We also did not examine the impact

of nausea and vomiting on medication adherence as adherence was high among our study participants. Only three participants failed to take their medication in the previous three days. Adherence has been reported to vary over time [452,543] and our adherence assessment may be hindered by our short period of follow up. Future studies should examine the effect of adverse events reported by individuals taking multiple medications on long-term medication adherence.

Participants taking cART with an EI-AED generally reported more symptoms at baseline than participants initiating cART, and participants taking neither cART nor an EI-AED despite having a higher $CD4^+$ T-cell count. This was likely influenced by medication use as well as underlying illness at the time of interview. Nineteen participants (95%) in the cART+EI-AED group were already taking cART or an EI-AED at the time of interview and ten participants (50%) had experienced a seizure in the previous 24 hours. We sought to limit the impact of these factors on assessments by conducting paired analyses for individuals in the cART+EI-AED and cART-only groups.

Self-report of symptoms are inherently subjective and we aimed to minimize subjectivity by using pre-established definitions to grade adverse event severity and by asking participants to describe their symptoms instead of grading them independently. However, characterizing adverse events as they are experienced by people taking cART is essential as these are the symptoms that adversely affect medication adherence. As reported by Carreno et al. [422], more participants in our study reported adverse events when they were asked symptoms via checklist than when they were asked to report adverse events spontaneously. This lends support to the assertion that adverse events may be underreported in routine clinical settings [297,296].

Despite our small sample size and our inability to compare across all possible treatment groups due to an insufficient number of HIV-positive individuals initiating only EI-AEDs, we

found that people taking cART with an EI-AED generally report more symptoms at baseline and experience greater nausea and vomiting after initiating their treatment. Baseline symptoms and adverse events resulting from co-treatment with cART and EI-AEDs may adversely affect medication adherence and deserve further investigation.

# CHAPTER 6:

# SUMMARY, LIMITATIONS, AND FUTURE DIRECTIONS

## SUMMARY

Non-communicable diseases are the leading cause of death worldwide and disproportionately affect individuals residing in low- and middle-income countries [544,545]. Low- and middle-income countries bear a "double burden" of diseases [546] due to an increasing prevalence of non-communicable diseases [547,548] as well as continuing incidence of infectious diseases [547,5]. Although current estimates regarding the prevalence of multimorbidity in low- and middle-income countries is scant and largely limited to comorbid non-communicable diseases [549-551], physicians in this setting are managing patients with multiple communicable and non-communicable diseases with increasing frequency. Research from high-income countries suggests that individuals with multiple chronic conditions have decreased quality of life [552], increased depression [553,554], and increased healthcare costs [555,556] compared to individuals with only one chronic condition. In addition, the complex care required by patients with multiple medical conditions is often not feasible in resource-limited settings where non-physician health care workers are trained to meet basic health needs. Understanding the factors that contribute to adverse outcomes among individuals with multimorbidity are essential to improving patient health and decreasing health care costs.

HIV and epilepsy are both common conditions, especially in low-income settings where the majority of people with HIV and people with epilepsy reside [1,18,19,5]. Although the prevalence of comorbid HIV and epilepsy is not known, both conditions disproportionally effect young adults in low-income settings [18,7] and, as a result, the likelihood for comorbid disease is

great. To better understand the challenges faced by individuals with comorbid diseases in a low-income country, we examined the psychosocial and medical intersection of HIV and epilepsy in Zambia.

**Psychosocial Intersection of HIV and Epilepsy**

Disease-associated stigma has been well-characterized for HIV and epilepsy independently [182,55,50,84]. Despite this, interventions designed to decrease disease-associated stigma have been met with varied success [557,558,366,559]. This may be due, in part, to limitations of the instruments used to assess stigma as well as unmeasured confounding variables, such as comorbid stigmatized medical conditions.

As part of this dissertation, we used item response theory to examine the performance of the Stigma Scale of Epilepsy (SSE) [233] in Zambia. This analysis indicated that the SSE assesses two underlying latent traits when administered to people with epilepsy. The first factor loaded questions inquiring about the difficulties faced by people with epilepsy and prejudices associated with epilepsy. The second factor included questions regarding the respondent's sentiments when he witnesses a seizure and how the respondent believes that people with epilepsy feel. Felt stigma is comprised of anticipated and internalized stigma [53,54]. Anticipated stigma, which describes an individual with epilepsy's fear that he/she will encounter stigma, was captured by items loading onto the first factor. Internalized stigma, which is comprised of the self-stigmatization associated with epilepsy, aligned well with items loading onto the second factor. Items from Jacoby's 3-item Stigma Scale loaded onto the first factor, indicating that this commonly used instrument does not assess both latent traits associated with felt stigma. The SSE may have wider utility than other stigma measures both because it more

completely captures felt stigma and because it was designed to also assess enacted stigma when administered to the general public [233].

We then used the SSE, along with the HIV/AIDS Stigma Instrument-PLWA and Jacoby's 3-item Stigma Scale, to examine layered stigma among people with comorbid HIV and epilepsy in Zambia. We examined whether comorbid HIV and epilepsy increased reports of HIV-related and epilepsy-associated stigma by administering these disease-specific instruments to people with HIV & epilepsy, people with HIV only, and people with epilepsy only who were recruited from local clinics.

Comorbid HIV and epilepsy moderately increased HIV-reported stigma. People with HIV & epilepsy were more likely to report feeling that other people blamed them for their HIV status than people with HIV only. People with HIV & epilepsy were also more likely than people with HIV only to report feeling that they were no longer a person because of their HIV status. Reported epilepsy-associated stigma was high and not significantly different among people with HIV & epilepsy and people with epilepsy only. This may be because 75% of people with HIV & epilepsy interviewed as part of this study were diagnosed with epilepsy prior to HIV. Unfortunately, our sample size was too small to investigate whether order of diagnosis influences reports of disease-associated stigma.

This study was among the first to investigate layered stigma resulting from comorbid infectious and non-communicable diseases. Previous research examining layered stigma have examined stigma from two infectious diseases [80,245,246] or layered stigma from the perspective of the general public [247]. Deribew et al. found that the presence of TB coinfection increased reported HIV-related stigma [245]. However, this is most likely related to TB's

association with underlying HIV infection [246] and, therefore, findings may have been a manifestation of HIV-related stigma instead of layered stigma.

This study also characterizes the patient population with comorbid HIV and epilepsy. Previous research reported that people with epilepsy are a vulnerable population in Zambia [560,184]. This study lends further support to this assertion as people with HIV & epilepsy were diagnosed with HIV at a younger age than people with HIV only. In addition, seizure frequency was greater among people with HIV & epilepsy than among people with epilepsy only. This may be a manifestation of AED treatment failure due to drug interactions with ARVs. Seventy percent of people with HIV and epilepsy interviewed were taking an ARV/AED combination that may result in ARV treatment failure [353].

**Medical Intersection of HIV and Epilepsy**

ARV-associated adverse events have been well-described. However, little is known about the frequency and severity of adverse events that result when first-line ARVs are combined with first-generation AEDs, which are often the only seizure medications available in low-income settings. The efficacy of EI-AEDs is also questionable. Studies generally agree that EI-AEDs, like phenobarbital, are as effective as other first-line AEDs for managing tonic-clonic seizures [398,399,311,400-403]. However, observational studies in low-income settings suggest that phenobarbital is well-tolerated [331,330,329] whereas randomized trials have shown mixed results when compared to other AEDs [402,410,411,403,412,311]. Few data have been published regarding patient-reported adverse events among people with epilepsy taking EI-AEDs in routine clinical settings in low-income countries.

As part of this dissertation, we conducted a cross-sectional study to examine patient-reported adverse events among 35 people with epilepsy obtaining phenobarbital as a part of routine clinical care in rural Zambia. Using the Liverpool Adverse Events Profile, participants reported a mean of 5 symptoms and a mean total side effects score of 28/76. All participants reported at least one adverse event in the previous four weeks. Over half reported sleepiness and dizziness. Memory problems and depression were also common. Total side effects score was not associated with age, gender, or phenobarbital dose. Side effects were also not associated with decreased medication adherence in this population.

Although these data were drawn from a small, convenience sample, it suggests that the prevalence of phenobarbital-associated adverse events may be higher in routine clinical settings than previously reported as part of observational trials in low-income countries. Interestingly, reported total side effects scores were still lower than scores reported by individuals in the United States and United Kingdom who were taking AEDs that are traditionally better tolerated. This suggests that people with epilepsy in low income settings may be willing to tolerate and even underreport adverse events if limited treatment options are available and if they believe that phenobarbital effectively controls their seizures. However, the cross-sectional nature of this data limits its generalizability as symptom causality could not be determined.

We then assessed patient-reported adverse events among HIV-positive individuals initiating concurrent treatment with combination antiretroviral therapy (cART) and an EI-AED (cART+EI-AED) compared to individuals initiating only cART (cART-only), individuals taking neither cART nor an EI-AED (Untreated). Adverse events were assessed by spontaneous report and checklist. For individuals in the cART+EI-AED and cART-only groups, adverse events were assessed at baseline and again two weeks later. As reported previously [422], participants

identified more side effects when adverse advents were assessed by checklist than by spontaneous report. We found that participants in the cART+EI-AED group generally reported more symptoms at baseline than individuals in the other three treatment groups. Increased nausea and vomiting was also reported by individuals in the cART+EI-AED after initiating treatment. No significant differences in adverse events were reported by individuals initiating only cART. The effect of nausea and vomiting on self-reported medication adherence was not assessed as adherence was generally high for all participants.

This study was one of the first to assess patient-reported adverse events among individuals taking concurrent medications for HIV and seizure. It suggests that simultaneous use of cART with an EI-AED may be associated with increased side effects that may adversely impact adherence among these patients. However, our patient follow up was not long enough to formally assess this.

### LIMITATIONS

Research for this dissertation was conducted in one country with a small number of patients who were already obtaining clinical care. Therefore, findings may not be generalizable to people with HIV and epilepsy outside of Zambia or to people in Zambia who do not have access to care. However, the findings from this dissertation suggest that additional investigation into layered stigma and adverse events resulting from concurrent medication usage are necessary, as both disease-associated stigma and cART and EI-AED-related side effects have been reported worldwide.

This dissertation may not have completely captured layered stigma resulting from comorbid HIV and epilepsy as the disease-specific stigma instruments used to assess layered

stigma in Chapter 3 were neither designed nor validated for this purpose. In addition, patient-reported adverse events may have been underestimated due to the limited number of adverse events we directly queried.

## FUTURE DIRECTIONS

This dissertation examined two patient-level traits that may be increased among individuals with multiple chronic conditions. Both disease-associated stigma and drug-related adverse events have been associated with decreased quality of life [152,218,220,200,202] as well as increased depression [95,154,158,159,148,228,225,359] and may contribute to the adverse outcomes seen among patients with multimorbidity. Both disease-associated stigma and drug-related adverse events are often underappreciated by existing literature and, as a result, this dissertation may serve as a starting point for future research related both to HIV and epilepsy as well as other comorbid diseases.

To advance our understanding of epilepsy-associated stigma, future studies should examine the latent traits assessed by the Stigma Scale of Epilepsy (SSE) when it is administered to the general public and to people with epilepsy in other settings. If this instrument is found to be a valid measure when used with both populations, it may help elucidate determinants of stigma that could be applicable to other stigmatized conditions and effectively targeted with stigma reduction interventions.

Most instruments validated to assess disease-associated stigma are condition specific. Although this may improve the sensitivity of stigma estimates, generic instruments to assess stigma would permit comparisons across conditions. Since the initiation of this research, instruments have been validated to compare stigma across conditions [561,249] yet, to the best of

our knowledge, there are currently no instruments which specifically assess layered stigma resulting from comorbid stigmatized conditions. Validating a generic instrument to assess layered stigma resulting from a wide variety of comorbid conditions would provide a valuable opportunity to assess layered stigma and examine factors, such as order of diagnoses, which may impact stigma experiences. Future investigations into layered stigma, whether related to HIV and epilepsy or other medical conditions, should highlight this often overlooked aspect of disease-associated stigma.

Much can be done to improve our understanding of patient-reported side effects among individuals taking cART in conjunction with EI-AEDs. A better characterization of EI-AED-associated adverse events obtained as part of routine clinical care in low-income countries is essential. This could be done by assessing the change in adverse events reported at baseline and at subsequent follow up visits among people with epilepsy initiating treatment with EI-AEDs. In addition, a larger cohort study of individuals initiating: cART with an EI-AED, cART only, and an EI-AED only would be valuable. Following this cohort for more than two weeks would permit extensive assessments of patient-reported adverse events and medication adherence at multiple time points and would shed light on how adverse events change over time.

As the availability of cART continues to increase worldwide and HIV-positive individuals continue to live longer, the number of individuals affected by layered stigma and adverse events resulting from concurrent medical treatments will likely increase. Further investigation into these issues is warranted given their potential impact on individual and population health.

# APPENDIX

**Table A.1: Adverse Event Grading Criteria**

| Symptom | Mild | Moderate | Severe |
|---|---|---|---|
| *Rash* | Rash on only one part of the body that went away without any treatment | Rash on only one part of the body that required treatment or a rash on more than one part of the body that went away without treatment | Rash on more than one part of the body that required treatment, hospitalization or resulted in death |
| *Diarrhea* | 1 or 2 episodes of unformed stools OR an increase of less than 3 formed stools over normal frequency in a 24-hour period | 3 or more episodes of unformed to watery stools OR increase of 4-6 formed stools over baseline per 24-hour period | Bloody diarrhea OR increase of more than 7 formed stools per 24-hour period OR increase in stool frequency requiring IV fluid replacement |
| *Nausea/Vomiting* | 1 or 2 episodes of nausea, or vomiting with minimal interference with oral intake | More than 2 episodes of nausea, or vomiting with decreased oral intake. Vomiting causes no or mild dehydration | Vomiting that requires IV rehydration |
| *Abdominal Pain* | Pain or constipation that is present but does not limit activities | Pain or constipation that limits your ability to work, enjoy activities with friends or travel | Pain or constipation that limits eating, movement, or your ability to care for yourself |
| *Vertigo* | Noticeable feeling of spinning while not moving that doesn't interfere with your activities | Feeling of movement that limits your ability to work, activities with friends or travel | Feeling of movement that limits your ability to feed yourself, bath and otherwise care for yourself |
| *Fatigue* | Tiredness that is relieved by rest | Tiredness that is not relieved by rest and limits your ability to work, participate in leisure activities and travel | Tiredness that is not relieved by rest and limits your ability to feed yourself, bath and otherwise care for yourself |
| *Headache* | Noticeable pain that does not interfere with daily activities | Headache limits your ability to work, participate in leisure activities and travel | Persistent pain that interferes with your ability to care for yourself |

**Table A.1 (cont'd)**

| Symptom | Mild | Moderate | Severe |
|---|---|---|---|
| *Unsteady Gait /Ataxia* | Visible unsteadiness, but does not interfere with activities | Needs a cane or other assistance to walk | Cannot walk even with assistance |
| *Vision problems* | Noticeable double vision or blurred vision, but does not interfere with activities | Double or blurred vision limits your ability to work, participate in leisure activities and travel | Double or blurred vision that interferes with your ability to care for yourself |
| *Weakness in Arms/Legs* | Noticeable weakness that doesn't interfere with activities | Weakness in arms and legs that limits your ability to work, cook, participate in leisure activities or travel | Weakness in arms and legs that limits your ability to feed yourself, bath or otherwise care for yourself |
| *Numbness/Tingling* | Noticeable numbness or tingling that do not interfere with activities | Numbness or tingling that interferes with your ability to work, participate in leisure activities or travel | Numbness or tingling that limits your ability to feed yourself, bath, sleep, or otherwise care for yourself |
| *General Weakness* | Noticeable weakness that is not limited to arms and legs but does not interfere with activities | Weakness that is not limited to arms and legs (is "all over") and interferes with your work, leisure activities or ability to travel | Disabling weakness that is "all over" and limits your ability to get out of bed without help, bath or otherwise care for yourself |
| *Problems thinking/ thinking too slowly* | Noticeable in either concentration or mental speed but does not interfere with activities | Change in concentration or mental slowness that limit your ability to talk to others, work or do other leisure activities at the same speed you used to | Change in concentration or mental slowness that limit your ability to feed yourself, bath or otherwise care for yourself |
| *Memory Problems* | Noticeable problems remembering things that do not interfere with function | Problems remembering things that limits ability to work, participate in leisure activities and travel | Memory impairment that limits your ability to feed yourself, bath or otherwise care for yourself |

**Table A.1 (cont'd)**

| Symptom | Mild | Moderate | Severe |
|---|---|---|---|
| *Irritability, getting angry too easily* | Becomes irritated or angry more easily or being more aggressive than in the past, but you can calm yourself down quickly and it doesn't interfere with activities | Becomes irritated/angry/aggressive more easily than in the past, You can calm yourself down, but the anger/irritability interferes with activities. | Irritability, anger or aggression from which you can't calm yourself down |
| *Low mood, depression, sadness* | Noticeable symptoms but does not interfere with activities | Symptoms decrease ability to work, participate in leisure activities or travel | Symptoms decrease ability to care for yourself OR behavior potentially harmful to yourself or others |
| *Other:* _____ | Present, but does not interfere with activities | Symptoms decrease ability to work, participate in leisure activities or travel | Symptoms limit your ability to feed yourself, bath or otherwise care for yourself |

# REFERENCES

## REFERENCES


**1. Ortblad, K. F., Lozano, R., & Murray, C. J. (2013). The burden of HIV: insights from the GBD 2010. *AIDS*, doi:10.1097/QAD.0b013e328362ba67.**

**2. UNAIDS (2013). UNAIDS Report on the Global AIDS Epidemic 2013. *Global Report*. New York: UNAIDS.**

**3. UNAIDS (2012). Together we will end AIDS. (pp. 135). Geneva: UNAIS.**

**4. Lozano, R., Naghavi, M., Foreman, K., Lim, S., Shibuya, K., Aboyans, V., et al. (2012). Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet, 380*(9859), 2095-2128, doi:10.1016/S0140-6736(12)61728-0.**

**5. Vos, T., Flaxman, A. D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M., et al. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet, 380*(9859), 2163-2196, doi:10.1016/S0140-6736(12)61729-2.**

**6. Mulissa, Z., Jerene, D., & Lindtjorn, B. (2010). Patients present earlier and survival has improved, but pre-ART attrition is high in a six-year HIV cohort data from Ethiopia. *PLoS One, 5*(10), e13268, doi:10.1371/journal.pone.0013268.**

**7. WHO (2011). Global HIV/AIDS Response: Epidemic update and health sector progress towards Universal Access, progress report 2011. (pp. 224). Geneva: World Health Organization.**

**8. Beyrer, C., & Abdool Karim, Q. (2013). The changing epidemiology of HIV in 2013. *Curr Opin HIV AIDS, 8*(4), 306-310, doi:10.1097/COH.0b013e328361f53a.**

**9. WHO (2013). Global update on HIV treatment 2013: results, impact, and opportunities. Geneva: WHO.**

**10. WHO (2010). Preventing mother-to-child transmission of HIV to reach the UNGASS and Millennium Development GOals. *Strategic Vision 2010-2015*. Geneva: WHO.**

**11. Masia, M., Padilla, S., Alvarez, D., Lopez, J. C., Santos, I., Soriano, V., et al. (2013). Risk, predictors, and mortality associated with non-AIDS events in newly diagnosed HIV-infected patients: role of antiretroviral therapy. *AIDS, 27*(2), 181-189, doi:10.1097/QAD.0b013e32835a1156.**

**12. Deeks, S. G., & Phillips, A. N. (2009). HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. *BMJ, 338*, a3172, doi:10.1136/bmj.a3172.**

**13. Diop, A. G., de Boer, H. M., Mandlhate, C., Prilipko, L., & Meinardi, H. (2003). The global campaign against epilepsy in Africa. *Acta Trop, 87*(1), 149-159, doi:S0001706X0300038X [pii].**

**14. Ngugi, A. K., Bottomley, C., Kleinschmidt, I., Sander, J. W., & Newton, C. R. (2010). Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. *Epilepsia, 51*(5), 883-890, doi:EPI2481 [pii] 10.1111/j.1528-1167.2009.02481.**

**15. Kellinghaus, C., Engbring, C., Kovac, S., Moddel, G., Boesebeck, F., Fischera, M., et al. (2008). Frequency of seizures and epilepsy in neurological HIV-infected patients. *Seizure, 17*(1), 27-33, doi:10.1016/j.seizure.2007.05.017.**

**16. Wong, M. C., Suite, N. D., & Labar, D. R. (1990). Seizures in human immunodeficiency virus infection. *Arch Neurol, 47*(6), 640-642.**

**17. Holtzman, D. M., Kaku, D. A., & So, Y. T. (1989). New-onset seizures associated with human immunodeficiency virus infection: causation and clinical features in 100 cases. *Am J Med, 87*(2), 173-177.**

**18. Newton, C. R., & Garcia, H. H. (2012). Epilepsy in poor regions of the world. *Lancet, 380*(9848), 1193-1201, doi:10.1016/S0140-6736(12)61381-6.**

**19. Yemadje, L. P., Houinato, D., Quet, F., Druet-Cabanac, M., & Preux, P. M. (2011). Understanding the differences in prevalence of epilepsy in tropical regions. *Epilepsia, 52*(8), 1376-1381, doi:10.1111/j.1528-1167.2011.03099.x.**

**20. Carpio, A., Bharucha, N. E., Jallon, P., Beghi, E., Campostrini, R., Zorzetto, S., et al. (2005). Mortality of epilepsy in developing countries. *Epilepsia, 46 Suppl 11*, 28-32, doi:10.1111/j.1528-1167.2005.00404.x.**

**21. Diop, A. G., Hesdorffer, D. C., Logroscino, G., & Hauser, W. A. (2005). Epilepsy and mortality in Africa: a review of the literature. *Epilepsia, 46 Suppl 11*, 33-35, doi:10.1111/j.1528-1167.2005.00405.x.**

**22. Tomson, T. (2006). Excess mortality in epilepsy in developing countries. *Lancet Neurol, 5*(10), 804-805, doi:10.1016/S1474-4422(06)70555-5.**

**23. Ding, D., Hong, Z., Wang, W. Z., Wu, J. Z., de Boer, H. M., Prilipko, L., et al. (2006). Assessing the disease burden due to epilepsy by disability adjusted life year in rural China. *Epilepsia, 47*(12), 2032-2037, doi:10.1111/j.1528-1167.2006.00802.x.**

**24. Watts, A. E. (1992). The natural history of untreated epilepsy in a rural community in Africa. *Epilepsia, 33*(3), 464-468.**

**25. WHO (2005). Global Campaign Against Epilepsy Atlas. Geneva.**

**26. Mbuba, C. K., Ngugi, A. K., Fegan, G., Ibinda, F., Muchohi, S. N., Nyundo, C., et al. (2012). Risk factors associated with the epilepsy treatment gap in Kilifi, Kenya: a cross-sectional study. *Lancet Neurol, 11*(8), 688-696, doi:10.1016/S1474-4422(12)70155-2.**

**27. Meyer, A. C., Dua, T., Ma, J., Saxena, S., & Birbeck, G. (2010). Global disparities in the epilepsy treatment gap: a systematic review. *Bull World Health Organ, 88*(4), 260-266, doi:10.2471/BLT.09.064147.**

**28. Scott, R. A., Lhatoo, S. D., & Sander, J. W. (2001). The treatment of epilepsy in developing countries: where do we go from here? *Bull World Health Organ, 79*(4), 344-351, doi:S0042-96862001000400012 [pii].**

**29. de Boer, H. M., Engel, J., Jr., & Prilipko, L. L. (2005). "Out of the shadows": a partnership that brings progress! *Epilepsia, 46 Suppl 1*, 61-62, doi:EPI461020 [pii] 10.1111/j.0013-9580.2005.461020.x.**

**30. WHO (2003). Global Campaign Against Epilepsy: Out of the Shadows. Geneva.**

**31. Chisholm, D., & Saxena, S. (2012). Cost effectiveness of strategies to combat neuropsychiatric conditions in sub-Saharan Africa and South East Asia: mathematical modelling study. *BMJ, 344*, e609, doi:10.1136/bmj.e609.**

**32. Hovinga, C. A., Asato, M. R., Manjunath, R., Wheless, J. W., Phelps, S. J., Sheth, R. D., et al. (2008). Association of non-adherence to antiepileptic drugs and seizures, quality of life, and productivity: survey of patients with epilepsy and physicians. *Epilepsy Behav, 13*(2), 316-322, doi:10.1016/j.yebeh.2008.03.009.**

**33. Faught, E., Duh, M. S., Weiner, J. R., Guerin, A., & Cunnington, M. C. (2008). Nonadherence to antiepileptic drugs and increased mortality: findings from the RANSOM Study. *Neurology, 71*(20), 1572-1578, doi:10.1212/01.wnl.0000319693.10338.b9.**

**34. Roullet, E. (1999). Opportunistic infections of the central nervous system during HIV-1 infection (emphasis on cytomegalovirus disease). *J Neurol, 246*(4), 237-243.**

**35. Satishchandra, P., Nalini, A., Gourie-Devi, M., Khanna, N., Santosh, V., Ravi, V., et al. (2000). Profile of neurologic disorders associated with HIV/AIDS from Bangalore, south India (1989-96). *Indian J Med Res, 111*, 14-23.**

**36. Schutte, C. M. (2013). Analysis of HIV-related mortality data in a tertiary South African neurology unit, 2006- 2012. *Southern African Journal of HIV Medicine, 14*(3), 121, doi:10.7196/sajhivmed.956.**

**37. Holmberg, S. D., Buchbinder, S. P., Conley, L. J., Wong, L. C., Katz, M. H., Penley, K. A., et al. (1995). The Spectrum of Medical Conditions and Symptoms before Acquired Immunodeficiency Syndrome in Homosexual and Bisexual Men Infected with the Human Immunodeficiency Virus. *American Journal of Epidemiology, 141*(5), 395-404.**

**38. Chadha, D. S., Handa, A., Sharma, S. K., Varadarajulu, P., & Singh, A. P. (2000). Seizures in patients with human immunodeficiency virus infection. *J Assoc Physicians India, 48*(6), 573-576.**

**39. Modi, G., Hari, K., Modi, M., & Mochan, A. (2007). The frequency and profile of neurology in black South African HIV infected (clade C) patients - a hospital-based prospective audit. *J Neurol Sci, 254*(1-2), 60-64, doi:S0022-510X(07)00022-6 [pii]10.1016/j.jns.2007.01.001.**

**40. Isezuo, S. A., Sani, A. Z., Ezunu, E., Maiyaki, S., Njoku, C. H., & Obembe, A. (2009). Clinical neuropathy in HIV/AIDS: an eight-year review of hospitalized patients in Sokoto, northwestern Nigeria. *Trop Doct, 39*(3), 133-135, doi:39/3/133 [pii] 10.1258/td.2008.080313.**

**41. Gongora-Rivera, F., Santos-Zambrano, J., Moreno-Andrade, T., Calzada-Lopez, P., & Soto-Hernandez, J. L. (2000). The clinical spectrum of neurological manifestations in AIDS patients in Mexico.** ***Arch Med Res, 31*****(4), 393-398, doi:S0188-4409(00)00067-9 [pii].**

**42. Sander, J. W. (2003). The natural history of epilepsy in the era of new antiepileptic drugs and surgical treatment.** ***Epilepsia, 44 Suppl 1*****, 17-20.**

**43. Weiner, B., Perry, R. P., & Magnusson, J. (1988). An attributional analysis of reactions to stigmas.** ***J Pers Soc Psychol, 55*****(5), 738-748.**

**44. Goffman, E. (1963).** ***Stigma: Notes on the Managment of Spoiled Identity*****. New York: Simon & Schuster, Inc.**

**45. Scambler, G. (2009). Health-related stigma.** ***Sociol Health Illn, 31*****(3), 441-455, doi:SHIL1161 [pii]10.1111/j.1467-9566.2009.01161.x.**

**46. Link, B. G., & Phelan, J. C. (2006). Stigma and its public health implications.** ***Lancet, 367*****(9509), 528-529, doi:S0140-6736(06)68184-1 [pii]10.1016/S0140-6736(06)68184-1.**

**47. Scambler, G. (2004). Re-framing Stigma: Felt and Enacted Stigma and Challenges to the Sociology of Chronic and Disabling Conditions.** ***Social Theory & Health, 2*****(1), 29-46, doi:10.1057/palgrave.sth.8700012.**

**48. Deacon, H. (2006). Towards a sustainable theory of health-related stigma: lessons from the HIV/AIDS literature.** ***Journal of Community & Applied Social Psychology, 16*****(6), 418-425, doi:10.1002/casp.900.**

**49. Scambler, G., & Hopkins, A. (1986). Being epileptic: coming to terms with stigma.** ***Sociology of Health & Illness, 8*****(1), 26-43.**

**50. Earnshaw, V. A., & Chaudoir, S. R. (2009). From conceptualizing to measuring HIV stigma: a review of HIV stigma mechanism measures.** ***AIDS Behav, 13*****(6), 1160-1177, doi:10.1007/s10461-009-9593-3.**

**51. Misir, P. (2013). Structuration Theory: A Conceptual Framework for HIV/AIDS Stigma.** ***J Int Assoc Provid AIDS Care*****, doi:10.1177/1545109712463072.**

**52. Link, B., & Phelan, J. C. (2001). Conceptualizing Stigma.** ***Annual Reviews in Sociology, 27*****, 363-385.**

**53. Scrambler, G., & Hopkins, A. (1986). Being epileptic: coming to terms with stigma.** ***Sociology of Health & Illness, 8*****(1), 26-43.**

**54. Jacoby, A. (1994). Felt versus enacted stigma: a concept revisited. Evidence from a study of people with epilepsy in remission.** ***Social science & medicine, 38*****(2), 269-274.**

**55. Jacoby, A. (2008). Epilepsy and stigma: an update and critical review.** ***Current neurology and neuroscience reports, 8*****(4), 339-344.**

**56. Steward, W. T., Herek, G. M., Ramakrishna, J., Bharat, S., Chandy, S., Wrubel, J., et al. (2008). HIV-related stigma: adapting a theoretical framework for use in India.** ***Soc Sci Med, 67*****(8), 1225-1235, doi:10.1016/j.socscimed.2008.05.032.**

**57. Muhlbauer, S. (2002). Experience of stigma by families with mentally ill members.** ***Journal of the American Psychiatric Nurses Association, 8*****, 76-83.**

**58. Quinn, D., & Earnshaw, V. (2011). Understanding Concealable Stigmatized Identities: The Role of Identity in Psychological, Physical, and Behavioral Outcomes.** ***Social Issues and Policy Review, 5*****(1), 160-190.**

**59. Crocker, J., & Major, B. (1989). Social Stigma and Self-Esteem: The Self-Protective Proprierties of Stigma.** ***Psychological Review, 96*****(4), 608-630.**

**60. Schneider, J. W., & Conrad, P. (1981). Medical and sociological typologies: the case of epilepsy.** ***Soc Sci Med A, 15*****(3 Pt 1), 211-219.**

**61. Reis, R., & Meinardi, H. (2002). ILAE/WHO "Out of the Shadows Campaign" Stigma: does the flag identify the cargo?** ***Epilepsy Behav, 3*****(6S2), 33-37.**

**62. DiIorio, C., Osborne Shafer, P., Letz, R., Henry, T., Schomer, D. L., & Yeager, K. (2003). The association of stigma with self-management and perceptions of health care among adults with epilepsy.** ***Epilepsy Behav, 4*****(3), 259-267, doi:S1525505003001033 [pii].**

**63. Austin, J. K., MacLeod, J., Dunn, D. W., Shen, J., & Perkins, S. M. (2004). Measuring stigma in children with epilepsy and their parents: instrument development and testing. *Epilepsy Behav, 5*(4), 472-482, doi:10.1016/j.yebeh.2004.04.008.**

**64. Admi, H., & Shaham, B. (2007). Living with epilepsy: ordinary people coping with extraordinary situations. *Qual Health Res, 17*(9), 1178-1187, doi:10.1177/1049732307307548.**

**65. Kilinc, S., & Campbell, C. (2009). "It shouldn't be something that's evil, it should be talked about": a phenomenological approach to epilepsy and stigma. *Seizure, 18*(10), 665-671, doi:S1059-1311(09)00183-6 [pii]10.1016/j.seizure.2009.09.001.**

**66. Westbrook, L. E., Bauman, L. J., & Shinnar, S. (1992). Applying stigma theory to epilepsy: a test of a conceptual model. *J Pediatr Psychol, 17*(5), 633-649.**

**67. Ablon, J. (2002). The nature of stigma and medical conditions. *Epilepsy Behav, 3*(6S2), 2-9.**

**68. Hatzenbuehler, M. L., Phelan, J. C., & Link, B. G. (2013). Stigma as a fundamental cause of population health inequalities. *Am J Public Health, 103*(5), 813-821, doi:10.2105/AJPH.2012.301069.**

**69. Jacoby, A., Snape, D., & Baker, G. A. (2005). Epilepsy and social identity: the stigma of a chronic neurological disorder. *Lancet Neurol, 4*(3), 171-178, doi:S1474442205010148 [pii]10.1016/S1474-4422(05)01014-8.**

**70. Jacoby, A. (2002). Stigma, epilepsy, and quality of life. *Epilepsy Behav, 3*(6S2), 10-20.**

**71. Baskind, R., & Birbeck, G. L. (2005). Epilepsy-associated stigma in sub-Saharan Africa: the social landscape of a disease. *Epilepsy Behav, 7*(1), 68-73, doi:S1525-5050(05)00140-X [pii] 0.1016/j.yebeh.2005.04.009.**

**72. Van Brakel, W. H. (2006). Measuring health-related stigma--a literature review. *Psychol Health Med, 11*(3), 307-334, doi:10.1080/13548500600595160.**

**73. Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men--New York City and California (1981). *MMWR Morb Mortal Wkly Rep, 30*(25), 305-308.**

**74. Herek, G. M., & Glunt, E. K. (1988). An epidemic of stigma. Public reactions to AIDS. *Am Psychol, 43*(11), 886-891.**

**75. Petros, G., Airhihenbuwa, C. O., Simbayi, L., Ramlagan, S., & Brown, B. (2006). HIV/AIDS and 'othering' in South Africa: the blame goes on. *Cult Health Sex, 8*(1), 67-77, doi:10.1080/13691050500391489.**

**76. Kohi, T. W., Makoae, L., Chirwa, M., Holzemer, W. L., Phetlhu, D. R., Uys, L., et al. (2006). HIV and AIDS stigma violates human rights in five African countries. *Nurs Ethics, 13*(4), 404-415.**

**77. Fife, B. L., & Wright, E. R. (2000). The dimensionality of stigma: a comparison of its impact on the self of persons with HIV/AIDS and cancer. *J Health Soc Behav, 41*(1), 50-67.**

**78. Greene, K., & Banerjee, S. C. (2006). Disease-related stigma: comparing predictors of AIDS and cancer stigma. *J Homosex, 50*(4), 185-209, doi:10.1300/J082v50n04_08.**

**79. Mak, W. W., Mo, P. K., Cheung, R. Y., Woo, J., Cheung, F. M., & Lee, D. (2006). Comparative stigma of HIV/AIDS, SARS, and tuberculosis in Hong Kong. *Soc Sci Med, 63*(7), 1912-1922, doi:10.1016/j.socscimed.2006.04.016.**

**80. Lekas, H. M., Siegel, K., & Leider, J. (2011). Felt and enacted stigma among HIV/HCV-coinfected adults: the impact of stigma layering. *Qual Health Res, 21*(9), 1205-1219, doi:10.1177/1049732311405684.**

**81. Reidpath, D. D., & Chan, K. Y. (2005). A method for the quantitative analysis of the layering of HIV-related stigma. *AIDS Care, 17*(4), 425-432, doi:10.1080/09540120412331319769.**

**82. Herek, G. M. (2002). Thinking about AIDS and stigma: a psychologist's perspective. *J Law Med Ethics, 30*(4), 594-607.**

**83. Walkey, F. H., Taylor, A. J., & Green, D. E. (1990). Attitudes to AIDS: a comparative analysis of a new and negative stereotype. *Soc Sci Med, 30*(5), 549-552.**

**84. Mbonu, N. C., van den Borne, B., & De Vries, N. K. (2009). Stigma of People with HIV/AIDS in Sub-Saharan Africa: A Literature Review. *J Trop Med, 2009*, 145891, doi:10.1155/2009/145891.**

**85. Swendeman, D., Rotheram-Borus, M. J., Comulada, S., Weiss, R., & Ramos, M. E. (2006). Predictors of HIV-related stigma among young people living with HIV. *Health Psychol, 25*(4), 501-509, doi:10.1037/0278-6133.25.4.501.**

**86. Lekas, H. M., Siegel, K., & Schrimshaw, E. W. (2006). Continuities and discontinuities in the experiences of felt and enacted stigma among women with HIV/AIDS. *Qual Health Res, 16*(9), 1165-1190, doi:10.1177/1049732306292284.**

**87. Kelly, J. A., St Lawrence, J. S., Smith, S., Jr., Hood, H. V., & Cook, D. J. (1987). Stigmatization of AIDS patients by physicians. *Am J Public Health, 77*(7), 789-791.**

**88. Herek, G. M., & Capitanio, J. P. (1993). Public reactions to AIDS in the United States: a second decade of stigma. *Am J Public Health, 83*(4), 574-577.**

**89. Moneyham, L., Seals, B., Demi, A., Sowell, R., Cohen, L., & Guillory, J. (1996). Perceptions of stigma in women infected with HIV. *AIDS Patient Care STDS, 10*(3), 162-167.**

**90. Herek, G. M., Capitanio, J. P., & Widaman, K. F. (2002). HIV-related stigma and knowledge in the United States: prevalence and trends, 1991-1999. *Am J Public Health, 92*(3), 371-377.**

**91. Muyinda, H., Seeley, J., Pickering, H., & Barton, T. (1997). Social aspects of AIDS-related stigma in rural Uganda. *Health Place, 3*(3), 143-147.**

**92. Songwathana, P., & Manderson, L. (2001). Stigma and rejection: living with AIDS in villages in southern Thailand. *Med Anthropol, 20*(1), 1-23, doi:10.1080/01459740.2001.9966185.**

**93. Kalichman, S. C., & Simbayi, L. (2004). Traditional beliefs about the cause of AIDS and AIDS-related stigma in South Africa. *AIDS Care, 16*(5), 572-580, doi:10.1080/09540120410001716360.**

**94. Lee, M. B., Wu, Z., Rotheram-Borus, M. J., Detels, R., Guan, J., & Li, L. (2005). HIV-related stigma among market workers in China. *Health Psychol, 24*(4), 435-438, doi:10.1037/0278-6133.24.4.435.**

**95. Peltzer, K., & Ramlagan, S. (2011). Perceived stigma among patients receiving antiretroviral therapy: a prospective study in KwaZulu-Natal, South Africa. *AIDS Care, 23*(1), 60-68, doi:10.1080/09540121.2010.498864.**

**96. Dasgupta, S., Sullivan, P. S., Dasgupta, A., Saha, B., & Salazar, L. F. (2013). Stigma and access to HIV care among HIV-infected women in Kolkata, West Bengal. *J Int Assoc Provid AIDS Care, 12*(1), 44-49, doi:10.1177/1545109711401410.**

**97. Vanable, P. A., Carey, M. P., Blair, D. C., & Littlewood, R. A. (2006). Impact of HIV-related stigma on health behaviors and psychological adjustment among HIV-positive men and women. *AIDS Behav, 10*(5), 473-482, doi:10.1007/s10461-006-9099-1.**

**98. Stutterheim, S. E., Bos, A. E., Pryor, J. B., Brands, R., Liebregts, M., & Schaalma, H. P. (2011). Psychological and social correlates of HIV status disclosure: the significance of stigma visibility. *AIDS Educ Prev, 23*(4), 382-392, doi:10.1521/aeap.2011.23.4.382.**

**99. Brener, L., Callander, D., Slavin, S., & de Wit, J. (2013). Experiences of HIV stigma: the role of visible symptoms, HIV centrality and community attachment for people living with HIV. *AIDS Care, 25*(9), 1166-1173, doi:10.1080/09540121.2012.752784.**

**100. Colbert, A. M., Kim, K. H., Sereika, S. M., & Erlen, J. A. (2010). An examination of the relationships among gender, health status, social support, and HIV-related stigma. *J Assoc Nurses AIDS Care, 21*(4), 302-313, doi:10.1016/j.jana.2009.11.004.**

**101. Maman, S., Abler, L., Parker, L., Lane, T., Chirowodza, A., Ntogwisangu, J., et al. (2009). A comparison of HIV stigma and discrimination in five international sites: the influence of care and treatment resources in high prevalence settings. *Soc Sci Med, 68*(12), 2271-2278, doi:10.1016/j.socscimed.2009.04.002.**

**102. Castro, A., & Farmer, P. (2005). Understanding and addressing AIDS-related stigma: from anthropological theory to clinical practice in Haiti. *Am J Public Health, 95*(1), 53-59, doi:10.2105/AJPH.2003.028563.**

**103. Campbell, C., Skovdal, M., Madanhire, C., Mugurungi, O., Gregson, S., & Nyamukapa, C. (2011). "We, the AIDS people. . .": how antiretroviral therapy enables Zimbabweans living with HIV/AIDS to cope with stigma. *Am J Public Health, 101*(6), 1004-1010, doi:10.2105/AJPH.2010.202838.**

**104. Makoae, L. N., Portillo, C. J., Uys, L. R., Dlamini, P. S., Greeff, M., Chirwa, M., et al. (2009). The impact of taking or not taking ARVs on HIV stigma as reported by persons living with HIV infection in five African countries. *AIDS Care, 21*(11), 1357-1362, doi:10.1080/09540120902862576.**

**105. Nattabi, B., Li, J., Thompson, S. C., Orach, C. G., & Earnest, J. (2011). Factors associated with perceived stigma among people living with HIV/AIDS in post-conflict northern Uganda. *AIDS Educ Prev, 23*(3), 193-205, doi:10.1521/aeap.2011.23.3.193.**

**106. Roura, M., Urassa, M., Busza, J., Mbata, D., Wringe, A., & Zaba, B. (2009). Scaling up stigma? The effects of antiretroviral roll-out on stigma and HIV testing. Early evidence from rural Tanzania. *Sex Transm Infect, 85*(4), 308-312, doi:10.1136/sti.2008.033183.**

**107. Mahajan, A. P., Sayles, J. N., Patel, V. A., Remien, R. H., Sawires, S. R., Ortiz, D. J., et al. (2008). Stigma in the HIV/AIDS epidemic: a review of the literature and recommendations for the way forward. *AIDS, 22 Suppl 2*, S67-79, doi:10.1097/01.aids.0000327438.13291.62.**

**108. Hawkins, T. (2006). Appearance-related side effects of HIV-1 treatment. *AIDS Patient Care STDS, 20*(1), 6-18, doi:10.1089/apc.2006.20.6.**

**109. Fox, M. P., Mazimba, A., Seidenberg, P., Crooks, D., Sikateyo, B., & Rosen, S. (2010). Barriers to initiation of antiretroviral treatment in rural and urban areas of Zambia: a cross-sectional study of cost, stigma, and perceptions about ART. *J Int AIDS Soc, 13*, 8, doi:10.1186/1758-2652-13-8.**

**110. Gilbert, L., & Walker, L. (2010). 'My biggest fear was that people would reject me once they knew my status...': stigma as experienced by patients in an HIV/AIDS clinic in Johannesburg, South Africa. *Health Soc Care Community, 18*(2), 139-146, doi:10.1111/j.1365-2524.2009.00881.x.**

**111. Sorsdahl, K. R., Mall, S., Stein, D. J., & Joska, J. A. (2011). The prevalence and predictors of stigma amongst people living with HIV/AIDS in the Western Province. *AIDS Care, 23*(6), 680-685, doi:10.1080/09540121.2010.525621.**

**112. Tzemis, D., Forrest, J. I., Puskas, C. M., Zhang, W., Orchard, T. R., Palmer, A. K., et al. (2013). Identifying self-perceived HIV-related stigma in a population accessing antiretroviral therapy. *AIDS Care, 25*(1), 95-102, doi:10.1080/09540121.2012.687809.**

**113. Mugoya, G. C., & Ernst, K. (2013). Gender differences in HIV-related stigma in Kenya. *AIDS Care,* doi:10.1080/09540121.2013.808733.**

**114. Galvan, F. H., Davis, E. M., Banks, D., & Bing, E. G. (2008). HIV stigma and social support among African Americans. *AIDS Patient Care STDS, 22*(5), 423-436, doi:10.1089/apc.2007.0169.**

**115. Emlet, C. A. (2006). A comparison of HIV stigma and disclosure patterns between older and younger adults living with HIV/AIDS. *AIDS Patient Care STDS, 20*(5), 350-358, doi:10.1089/apc.2006.20.350.**

**116. Genberg, B. L., Hlavka, Z., Konda, K. A., Maman, S., Chariyalertsak, S., Chingono, A., et al. (2009). A comparison of HIV/AIDS-related stigma in four countries: negative attitudes and perceived acts of discrimination towards people living with HIV/AIDS. *Soc Sci Med, 68*(12), 2279-2287, doi:10.1016/j.socscimed.2009.04.005.**

**117. Boer, H., & Emons, P. A. (2004). Accurate and inaccurate HIV transmission beliefs, stigmatizing and HIV protection motivation in northern Thailand. *AIDS Care, 16*(2), 167-176, doi:10.1080/09540120410001641011.**

**118. Pearson, C. R., Micek, M. A., Pfeiffer, J., Montoya, P., Matediane, E., Jonasse, T., et al. (2009). One year after ART initiation: psychosocial factors associated with stigma among HIV-positive Mozambicans. *AIDS Behav, 13*(6), 1189-1196, doi:10.1007/s10461-009-9596-0.**

**119. Shamos, S., Hartwig, K. A., & Zindela, N. (2009). Men's and women's experiences with HIV and stigma in Swaziland. *Qual Health Res, 19*(12), 1678-1689, doi:10.1177/1049732309353910.**

**120. Joffe, H. l. n. (2003). Social Representation of AIDS among Zambian Adolescents. *J Health Psychol, 8*(5), 616-631, doi:10.1177/13591053030085011.**

**121. Duffy, L. (2005). Suffering, shame, and silence: the stigma of HIV/AIDS. *J Assoc Nurses AIDS Care, 16*(1), 13-20.**

**122. Sandelowski, M., Lambe, C., & Barroso, J. (2004). Stigma in HIV-positive women. *J Nurs Scholarsh, 36*(2), 122-128.**

**123. Sayles, J. N., Wong, M. D., & Cunningham, W. E. (2006). The inability to take medications openly at home: does it help explain gender disparities in HAART use? *J Womens Health (Larchmt), 15*(2), 173-181, doi:10.1089/jwh.2006.15.173.**

**124. Hasan, M. T., Nath, S. R., Khan, N. S., Akram, O., Gomes, T. M., & Rashid, S. F. (2012). Internalized HIV/AIDS-related stigma in a sample of HIV-positive people in Bangladesh. *J Health Popul Nutr, 30*(1), 22-30.**

**125. Rao, D., Pryor, J. B., Gaddist, B. W., & Mayer, R. (2008). Stigma, secrecy, and discrimination: ethnic/racial differences in the concerns of people living with HIV/AIDS. *AIDS Behav, 12*(2), 265-271, doi:10.1007/s10461-007-9268-x.**

**126. Yang, L. H., & Kleinman, A. (2008). 'Face' and the embodiment of stigma in China: the cases of schizophrenia and AIDS. *Soc Sci Med, 67*(3), 398-408, doi:10.1016/j.socscimed.2008.03.011.**

**127. Wolfe, W. R., Weiser, S. D., Bangsberg, D. R., Thior, I., Makhema, J. M., Dickinson, D. B., et al. (2006). Effects of HIV-related stigma among an early sample of patients receiving antiretroviral therapy in Botswana. *AIDS Care, 18*(8), 931-933, doi:10.1080/09540120500333558.**

**128. Babalola, S. (2007). Readiness for HIV testing among young people in northern Nigeria: the roles of social norm and perceived stigma. *AIDS Behav, 11*(5), 759-769, doi:10.1007/s10461-006-9189-0.**

**129. Pulerwitz, J., Michaelis, A. P., Lippman, S. A., Chinaglia, M., & Diaz, J. (2008). HIV-related stigma, service utilization, and status disclosure among truck drivers crossing the Southern borders in Brazil. *AIDS Care, 20*(7), 764-770, doi:10.1080/09540120701506796.**

**130. Sliep, Y., Poggenpoel, M., & Gmeiner, A. (2001). The experience of HIV reactive patients in rural Malawi--Part I. *Curationis, 24*(3), 56-65.**

**131. Kaplan, A. H., Scheyett, A., & Golin, C. E. (2005). HIV and stigma: analysis and research program. *Curr HIV/AIDS Rep, 2*(4), 184-188.**

**132. Greeff, M., & Phetlhu, R. (2007). The meaning and effect of HIV/AIDS stigma for people living with AIDS and nurses involved in their care in the North West Province, South Africa. *Curationis, 30*(2), 12-23.**

**133. Holzemer, W. L., Uys, L. R., Chirwa, M. L., Greeff, M., Makoae, L. N., Kohi, T. W., et al. (2007). Validation of the HIV/AIDS Stigma Instrument - PLWA (HASI-P). *AIDS Care, 19*(8), 1002-1012, doi:10.1080/09540120701245999.**

**134. Tarwireyi, F. (2005). Stigma and discrimination: coping behaviours of people living with HIV and AIDS in an urban community of Mabvuku and Tafara, Harare, Zimbabwe. *Cent Afr J Med, 51*(7-8), 71-76.**

**135. Kingori, C., Reece, M., Obeng, S., Murray, M., Shacham, E., Dodge, B., et al. (2012). Impact of internalized stigma on HIV prevention behaviors among HIV-infected individuals seeking HIV care in Kenya. *AIDS Patient Care STDS, 26*(12), 761-768, doi:10.1089/apc.2012.0258.**

**136. Chandra, P. S., Deepthivarma, S., & Manjula, V. (2003). Disclosure of HIV infection in south India: patterns, reasons and reactions. *AIDS Care, 15*(2), 207-215, doi:10.1080/0954012031000068353.**

**137. Smith, R., Rossetto, K., & Peterson, B. L. (2008). A meta-analysis of disclosure of one's HIV-positive status, stigma and social support. *AIDS Care, 20*(10), 1266-1275, doi:10.1080/09540120801926977.**

**138. Siegel, K., & Krauss, B. J. (1991). Living with HIV infection: adaptive tasks of seropositive gay men. *J Health Soc Behav, 32*(1), 17-32.**

**139. Liu, H., Hu, Z., Li, X., Stanton, B., Naar-King, S., & Yang, H. (2006). Understanding interrelationships among HIV-related stigma, concern about HIV infection, and intent to disclose HIV serostatus: a pretest-posttest study in a rural area of eastern China. *AIDS Patient Care STDS, 20*(2), 133-142, doi:10.1089/apc.2006.20.133.**

**140. Audet, C. M., McGowan, C. C., Wallston, K. A., & Kipp, A. M. (2013). Relationship between HIV stigma and self-isolation among people living with HIV in Tennessee. *PLoS One, 8*(8), e69564, doi:10.1371/journal.pone.0069564.**

**141. Holzemer, W. L., Uys, L., Makoae, L., Stewart, A., Phetlhu, R., Dlamini, P. S., et al. (2007). A conceptual model of HIV/AIDS stigma from five African countries. *J Adv Nurs, 58*(6), 541-551, doi:10.1111/j.1365-2648.2007.04244.x.**

**142. Campbell, C., Foulis, C. A., Maimane, S., & Sibiya, Z. (2005). "I have an evil child at my house": stigma and HIV/AIDS management in a South African community. *Am J Public Health, 95*(5), 808-815, doi:10.2105/AJPH.2003.037499.**

**143. Kinsler, J. J., Wong, M. D., Sayles, J. N., Davis, C., & Cunningham, W. E. (2007). The effect of perceived stigma from a health care provider on access to care among a low-income HIV-positive population. *AIDS Patient Care STDS, 21*(8), 584-592, doi:10.1089/apc.2006.0202.**

**144. Rintamaki, L. S., Davis, T. C., Skripkauskas, S., Bennett, C. L., & Wolf, M. S. (2006). Social stigma concerns and HIV medication adherence. *AIDS Patient Care STDS, 20*(5), 359-368, doi:10.1089/apc.2006.20.359.**

**145. Sanjobo, N., Frich, J. C., & Fretheim, A. (2008). Barriers and facilitators to patients' adherence to antiretroviral treatment in Zambia: a qualitative study. *SAHARA J, 5*(3), 136-143.**

**146. Dlamini, P. S., Wantland, D., Makoae, L. N., Chirwa, M., Kohi, T. W., Greeff, M., et al. (2009). HIV stigma and missed medications in HIV-positive people in five African countries. *AIDS Patient Care STDS, 23*(5), 377-387, doi:10.1089/apc.2008.0164.**

**147. Monjok, E., Smesny, A., Okokon, I. B., Mgbere, O., & Essien, E. J. (2010). Adherence to antiretroviral therapy in Nigeria: an overview of research studies and implications for policy and practice. *HIV AIDS (Auckl), 2*, 69-76.**

**148. Rao, D., Feldman, B. J., Fredericksen, R. J., Crane, P. K., Simoni, J. M., Kitahata, M. M., et al. (2012). A structural equation model of HIV-related stigma, depressive symptoms, and medication adherence. *AIDS Behav, 16*(3), 711-716, doi:10.1007/s10461-011-9915-0.**

**149. Weiser, S., Wolfe, W., Bangsberg, D., Thior, I., Gilbert, P., Makhema, J., et al. (2003). Barriers to antiretroviral adherence for patients living with HIV infection and AIDS in Botswana. *J Acquir Immune Defic Syndr, 34*(3), 281-288.**

**150. Talam, N. C., Gatongi, P., Rotich, J., & Kimaiyo, S. (2008). Factors affecting antiretroviral drug adherence among HIV/AIDS adult patients attending HIV/AIDS clinic at Moi Teaching and Referral Hospital, Eldoret, Kenya. *East Afr J Public Health, 5*(2), 74-78.**

**151. Greeff, M., Uys, L. R., Wantland, D., Makoae, L., Chirwa, M., Dlamini, P., et al. (2010). Perceived HIV stigma and life satisfaction among persons living with HIV infection in five African countries: a longitudinal study. *Int J Nurs Stud, 47*(4), 475-486, doi:10.1016/j.ijnurstu.2009.09.008.**

**152. Thomas, B. E., Rehman, F., Suryanarayanan, D., Josephine, K., Dilip, M., Dorairaj, V. S., et al. (2005). How stigmatizing is stigma in the life of people living with HIV: a study on HIV positive individuals from Chennai, South India. *AIDS Care, 17*(7), 795-801, doi:10.1080/09540120500099936.**

**153. Varni, S. E., Miller, C. T., McCuin, T., & Solomon, S. E. (2012). Disengagement and Engagement Coping with HIV/AIDS Stigma and Psychological Well-Being of People with HIV/AIDS. *J Soc Clin Psychol, 31*(2), 123-150.**

**154. Simbayi, L. C., Kalichman, S., Strebel, A., Cloete, A., Henda, N., & Mqeketo, A. (2007). Internalized stigma, discrimination, and depression among men and women living with HIV/AIDS in Cape Town, South Africa. *Soc Sci Med, 64*(9), 1823-1831, doi:10.1016/j.socscimed.2007.01.006.**

**155. Li, L., Lee, S. J., Thammawijaya, P., Jiraphongsa, C., & Rotheram-Borus, M. J. (2009). Stigma, social support, and depression among people living with HIV in Thailand. *AIDS Care, 21*(8), 1007-1013, doi:10.1080/09540120802614358.**

**156. Grov, C., Golub, S. A., Parsons, J. T., Brennan, M., & Karpiak, S. E. (2010). Loneliness and HIV-related stigma explain depression among older HIV-positive adults. *AIDS Care, 22*(5), 630-639, doi:10.1080/09540120903280901.**

**157. Akena, D., Musisi, S., Joska, J., & Stein, D. J. (2012). The association between aids related stigma and major depressive disorder among HIV-positive individuals in Uganda. *PLoS One, 7*(11), e48671, doi:10.1371/journal.pone.0048671.**

**158. Charles, B., Jeyaseelan, L., Pandian, A. K., Sam, A. E., Thenmozhi, M., & Jayaseelan, V. (2012). Association between stigma, depression and quality of life of people living with HIV/AIDS (PLHA) in South India - a community based cross sectional study. *BMC Public Health, 12*, 463, doi:10.1186/1471-2458-12-463.**

**159. Onyebuchi-Iwudibia, O., & Brown, A. (2013). HIV and depression in Eastern Nigeria: The role of HIV-related stigma. *AIDS Care*, doi:10.1080/09540121.2013.844761.**

**160. Nyblade, L. C. (2006). Measuring HIV stigma: existing knowledge and gaps. *Psychol Health Med, 11*(3), 335-345, doi:10.1080/13548500600595178.**

**161. Sowell, R. L., Lowenstein, A., Moneyham, L., Demi, A., Mizuno, Y., & Seals, B. F. (1997). Resources, stigma, and patterns of disclosure in rural women with HIV infection. *Public Health Nurs, 14*(5), 302-312.**

**162. Berger, B. E., Ferrans, C. E., & Lashley, F. R. (2001). Measuring stigma in people with HIV: psychometric assessment of the HIV stigma scale. *Res Nurs Health, 24*(6), 518-529.**

**163. Lee, R., Kochman, A., & Sikkema, K. (2002). Internalized stigma among people living with HIV-AIDS. *AIDS Behav, 6*(4), 309-319.**

**164. Clark, H. J., Lindner, G., Armistead, L., & Austin, B. J. (2003). Stigma, disclosure, and psychological functioning among HIV-infected and non-infected African-American women. *Women Health, 38*(4), 57-71.**

**165. Reece, M. (2003). HIV-related mental health care: factors influencing dropout among low-income, HIV-positive individuals. *AIDS Care, 15*(5), 707-716, doi:10.1080/09540120310001595195.**

**166. Bunn, J. Y., Solomon, S. E., Miller, C., & Forehand, R. (2007). Measurement of stigma in people with HIV: a reexamination of the HIV Stigma Scale. *AIDS Educ Prev, 19*(3), 198-208, doi:10.1521/aeap.2007.19.3.198.**

**167. Franke, M. F., Munoz, M., Finnegan, K., Zeladita, J., Sebastian, J. L., Bayona, J. N., et al. (2010). Validation and abbreviation of an HIV stigma scale in an adult spanish-speaking population in urban Peru. *AIDS Behav, 14*(1), 189-199, doi:10.1007/s10461-008-9474-1.**

**168. Wright, K., Naar-King, S., Lam, P., Templin, T., & Frey, M. (2007). Stigma scale revised: reliability and validity of a brief measure of stigma for HIV+ youth. *J Adolesc Health, 40*(1), 96-98, doi:10.1016/j.jadohealth.2006.08.001.**

**169. Sayles, J. N., Hays, R. D., Sarkisian, C. A., Mahajan, A. P., Spritzer, K. L., & Cunningham, W. E. (2008). Development and psychometric assessment of a multidimensional measure of internalized HIV stigma in a sample of HIV-positive adults. *AIDS Behav, 12*(5), 748-758, doi:10.1007/s10461-008-9375-3.**

**170. Van Rie, A., Sengupta, S., Pungrassami, P., Balthip, Q., Choonuan, S., Kasetjaroen, Y., et al. (2008). Measuring stigma associated with tuberculosis and HIV/AIDS in southern Thailand: exploratory and confirmatory factor analyses of two new scales. *Trop Med Int Health, 13*(1), 21-30, doi:10.1111/j.1365-3156.2007.01971.x.**

**171. Visser, M. J., Kershaw, T., Makin, J. D., & Forsyth, B. W. (2008). Development of parallel scales to measure HIV-related stigma. *AIDS Behav, 12*(5), 759-771, doi:10.1007/s10461-008-9363-7.**

**172. Kalichman, S. C., Simbayi, L. C., Cloete, A., Mthembu, P. P., Mkhonta, R. N., & Ginindza, T. (2009). Measuring AIDS stigmas in people living with HIV/AIDS: the Internalized AIDS-Related Stigma Scale. *AIDS Care, 21*(1), 87-93, doi:10.1080/09540120802032627.**

**173. Jimenez, J. C., Puig, M., Ramos, J. C., Morales, M., Asencio, G., Sala, A. C., et al. (2010). Measuring HIV felt stigma: a culturally adapted scale targeting PLWHA in Puerto Rico. *AIDS Care, 22*(11), 1314-1322, doi:10.1080/09540121003758481.**

**174. Birbeck, G., Kvalsund, M., Byers, P., Bradbury, R., Mang'ombe, C., Organek, N., et al. (2011). Neuropsychiatric and Socioeconomic Status Impact Antiretroviral Adherence and Mortality in Rural Zambia. *American Journal of Tropical Medicine and Hygiene, 85*(4), 782-789.**

**175. Zelaya, C. E., Sivaram, S., Johnson, S. C., Srikrishnan, A. K., Suniti, S., & Celentano, D. D. (2012). Measurement of self, experienced, and perceived HIV/AIDS stigma using parallel scales in Chennai, India. *AIDS Care, 24*(7), 846-855, doi:10.1080/09540121.2011.647674.**

**176. Jeyaseelan, L., Kumar, S., Mohanraj, R., Rebekah, G., Rao, D., & Manhart, L. E. (2013). Assessing HIV/AIDS stigma in south India: validation and abridgement of the Berger HIV Stigma scale. *AIDS Behav, 17*(1), 434-443, doi:10.1007/s10461-011-0128-3.**

**177. Kingori, C., Reece, M., Obeng, S., Murray, M., Shacham, E., Dodge, B., et al. (2013). Psychometric evaluation of a cross-culturally adapted felt stigma questionnaire among people living with HIV in Kenya. *AIDS Patient Care STDS, 27*(8), 481-488, doi:10.1089/apc.2012.0403.**

**178. Tsai, A. C., Weiser, S. D., Steward, W. T., Mukiibi, N. F., Kawuma, A., Kembabazi, A., et al. (2013). Evidence for the reliability and validity of the internalized AIDS-related stigma scale in rural Uganda. *AIDS Behav, 17*(1), 427-433, doi:10.1007/s10461-012-0281-3.**

**179. Jacoby, A. (1992). Epilepsy and the quality of everyday life. Findings from a study of people with well-controlled epilepsy. *Soc Sci Med, 34*(6), 657-666.**

**180. Birbeck, G. L., Kvalsund, M. P., Byers, P. A., Bradbury, R., Mang'ombe, C., Organek, N., et al. (2011). Neuropsychiatric and socioeconomic status impact antiretroviral adherence and mortality in rural Zambia. *Am J Trop Med Hyg, 85*(4), 782-789, doi:10.4269/ajtmh.2011.11-0187.**

**181. Mushi, D., Hunter, E., Mtuya, C., Mshana, G., Aris, E., & Walker, R. (2011). Social-cultural aspects of epilepsy in Kilimanjaro Region, Tanzania: knowledge and experience among patients and carers. *Epilepsy Behav, 20*(2), 338-343, doi:10.1016/j.yebeh.2010.11.016.**

**182. Fernandes, P. T., Snape, D. A., Beran, R. G., & Jacoby, A. (2011). Epilepsy stigma: what do we know and where next? *Epilepsy Behav, 22*(1), 55-62, doi:S1525-5050(11)00070-9 [pii]10.1016/j.yebeh.2011.02.014.**

**183. Al-Khateeb, J. M., & Al-Khateeb, A. J. (2013). Research on psychosocial aspects of epilepsy in Arab countries: A review of literature. *Epilepsy & Behavior*, doi:10.1016/j.yebeh.2013.09.033.**

**184. Atadzhanov, M., Haworth, A., Chomba, E. N., Mbewe, E. K., & Birbeck, G. L. (2010). Epilepsy-associated stigma in Zambia: what factors predict greater felt stigma in a highly stigmatized population? *Epilepsy Behav, 19*(3), 414-418, doi:S1525-5050(10)00551-2 [pii]10.1016/j.yebeh.2010.08.017.**

**185. Bhalla, D., Chea, K., Hun, C., Vannareth, M., Huc, P., Chan, S., et al. (2012). Population-based study of epilepsy in Cambodia associated factors, measures of impact, stigma, quality of life, knowledge-attitude-practice, and treatment gap. *PLoS One, 7*(10), e46296, doi:10.1371/journal.pone.0046296.**

**186. Adjei, P., Akpalu, A., Laryea, R., Nkromah, K., Sottie, C., Ohene, S., et al. (2013). Beliefs on epilepsy in Northern Ghana. *Epilepsy Behav, 29*(2), 316-321, doi:10.1016/j.yebeh.2013.07.034.**

**187. Ratsepp, M., Oun, A., Haldre, S., & Kaasik, A. E. (2000). Felt stigma and impact of epilepsy on employment status among Estonian people: exploratory study. *Seizure, 9*(6), 394-401, doi:10.1053/seiz.2000.0439 S1059-1311(00)90439-4 [pii].**

**188. Baker, G. A. (2002). People with epilepsy: what do they know and understand, and how does this contribute to their perceived level of stigma? *Epilepsy Behav, 3*(6S2), 26-32.**

**189. Baker, G. A., Brooks, J., Buck, D., & Jacoby, A. (2000). The stigma of epilepsy: a European perspective. *Epilepsia, 41*(1), 98-104.**

**190. Baker, G. A., Jacoby, A., Gorry, J., Doughty, J., & Ellina, V. (2005). Quality of life of people with epilepsy in Iran, the Gulf, and Near East. *Epilepsia, 46*(1), 132-140, doi:EPI20704 [pii] 10.1111/j.0013-9580.2005.20704.x.**

**191. Chaplin, J. E., Yepez Lasso, R., Shorvon, S. D., & Floyd, M. (1992). National general practice study of epilepsy: the social and psychological effects of a recent diagnosis of epilepsy. *BMJ, 304*(6839), 1416-1418.**

**192. Ryan, R., Kempner, K., & Emlen, A. C. (1980). The stigma of epilepsy as a self-concept. *Epilepsia, 21*(4), 433-444.**

**193. Jacoby, A., Baker, G. A., Steen, N., Potts, P., & Chadwick, D. W. (1996). The clinical course of epilepsy and its psychosocial correlates: findings from a U.K. Community study. *Epilepsia, 37*(2), 148-161.**

**194. Baker, G. A., Jacoby, A., Buck, D., Stalgis, C., & Monnet, D. (1997). Quality of life of people with epilepsy: a European study. *Epilepsia, 38*(3), 353-362.**

**195. Buck, D., Jacoby, A., Baker, G. A., Ley, H., & Steen, N. (1999). Cross-cultural differences in health-related quality of life of people with epilepsy: findings from a European study. *Qual Life Res, 8*(8), 675-685.**

**196. Lee, S. A., Yoo, H. J., Lee, B. I., & Korean Qo, L. i. E. S. G. (2005). Factors contributing to the stigma of epilepsy. *Seizure, 14*(3), 157-163, doi:10.1016/j.seizure.2005.01.001.**

**197. Smith, G., Ferguson, P. L., Saunders, L. L., Wagner, J. L., Wannamaker, B. B., & Selassie, A. W. (2009). Psychosocial factors associated with stigma in adults with epilepsy. *Epilepsy Behav, 16*(3), 484-490, doi:S1525-5050(09)00449-1 [pii] 10.1016/j.yebeh.2009.08.028.**

**198. Taylor, J., Baker, G. A., & Jacoby, A. (2011). Levels of epilepsy stigma in an incident population and associated factors. *Epilepsy Behav, 21*(3), 255-260, doi:10.1016/j.yebeh.2011.04.002.**

**199. Bielen, I., Friedrich, L., Sruk, A., Prvan, M. P., Hajnsek, S., Petelin, Z., et al. (2013). Factors associated with perceived stigma of epilepsy in Croatia: A study using the revised Epilepsy Stigma Scale. *Seizure,* doi:10.1016/j.seizure.2013.10.008.**

**200. Kumari, P., Ram, D., Haque Nizamie, S., & Goyal, N. (2009). Stigma and quality of life in individuals with epilepsy: a preliminary report. *Epilepsy Behav, 15*(3), 358-361, doi:S1525-5050(09)00289-3 [pii]10.1016/j.yebeh.2009.05.003.**

**201. Stevanovic, D. (2007). Health-related quality of life in adolescents with well-controlled epilepsy. *Epilepsy Behav, 10*(4), 571-575, doi:10.1016/j.yebeh.2007.02.015.**

**202. Jacoby, A., Snape, D., & Baker, G. A. (2009). Determinants of quality of life in people with epilepsy. *Neurol Clin, 27*(4), 843-863, doi:10.1016/j.ncl.2009.06.003.**

**203. Mbuba, C. K., Abubakar, A., Odermatt, P., Newton, C. R., & Carter, J. A. (2012). Development and validation of the Kilifi Stigma Scale for Epilepsy in Kenya. *Epilepsy & Behavior,* doi:S1525-5050(12)00085-6 [pii]10.1016/j.yebeh.2012.02.019.**

**204. Devinsky, O., Westbrook, L., Cramer, J., Glassman, M., Perrine, K., & Camfield, C. (1999). Risk factors for poor health-related quality of life in adolescents with epilepsy. *Epilepsia, 40*(12), 1715-1720.**

**205. Ghanean, H., Jacobsson, L., & Nojomy, M. (2013). Self-perception of stigma in persons with epilepsy in Tehran, Iran. *Epilepsy Behav, 28*(2), 163-167, doi:10.1016/j.yebeh.2013.04.009.**

**206. Onwuekwe, I. O., Onodugo, O. D., Ezeala-Adikaibe, B., Aguwa, E. N., Ejim, E. C., Ndukuba, K., et al. (2009). Pattern and presentation of epilepsy in Nigerian Africans: a study of trends in the southeast. *Trans R Soc Trop Med Hyg, 103*(8), 785-789, doi:10.1016/j.trstmh.2009.04.010.**

**207. Morrell, M. J. (2002). Stigma and epilepsy. *Epilepsy Behav, 3*(6S2), 21-25.**

**208. Tedman, S., Thornton, E., & Baker, G. (1995). Development of a scale to measure core beliefs and perceived self efficacy in adults with epilepsy. *Seizure, 4*(3), 221-231.**

**209. Hermann, B. P., Whitman, S., Wyler, A. R., Anton, M. T., & Vanderzwagg, R. (1990). Psychosocial predictors of psychopathology in epilepsy. *Br J Psychiatry, 156,* 98-105.**

**210. Funderburk, J. A., McCormick, B. P., & Austin, J. K. (2007). Does attitude toward epilepsy mediate the relationship between perceived stigma and mental health outcomes in children with epilepsy? *Epilepsy Behav, 11*(1), 71-76, doi:10.1016/j.yebeh.2007.04.006.**

**211. Paschal, A. M., Ablah, E., Wetta-Hall, R., Molgaard, C. A., & Liow, K. (2005). Stigma and safe havens: a medical sociological perspective on African-American female epilepsy patients. *Epilepsy Behav, 7*(1), 106-115, doi:10.1016/j.yebeh.2005.03.020.**

**212. Rafael, F., Houinato, D., Nubukpo, P., Dubreuil, C. M., Tran, D. S., Odermatt, P., et al. (2010). Sociocultural and psychological features of perceived stigma reported by people with epilepsy in Benin. *Epilepsia, 51*(6), 1061-1068, doi:EPI2511 [pii]10.1111/j.1528-1167.2009.02511.x.**

**213. Chong, J., Drake, K., Atkinson, P. B., Ouellette, E., & Labiner, D. M. (2012). Social and family characteristics of Hispanics with epilepsy. *Seizure, 21*(1), 12-16, doi:10.1016/j.seizure.2011.08.008.**

**214. Jacoby, A., Wang, W., Vu, T. D., Wu, J., Snape, D., Aydemir, N., et al. (2008). Meanings of epilepsy in its sociocultural context and implications for stigma: findings from ethnographic studies in local communities in China and Vietnam. *Epilepsy Behav, 12*(2), 286-297, doi:10.1016/j.yebeh.2007.10.006.**

**215. Bellon, M., Walker, C., Peterson, C., & Cookson, P. (2013). The "E" word: epilepsy and perceptions of unfair treatment from the 2010 Australian Epilepsy Longitudinal Survey. *Epilepsy Behav, 27*(1), 251-256, doi:10.1016/j.yebeh.2013.01.016.**

**216. Osakwe, C., Otte, W. M., & Alo, C. (2013). Epilepsy prevalence, potential causes and social beliefs in Ebonyi State and Benue State, Nigeria. *Epilepsy Res*, doi:10.1016/j.eplepsyres.2013.11.010.**

**217. Pal, S. K., Sharma, K., Prabhakar, S., & Pathak, A. (2008). Psychosocial, demographic, and treatment-seeking strategic behavior, including faith healing practices, among patients with epilepsy in northwest India. *Epilepsy Behav, 13*(2), 323-332, doi:10.1016/j.yebeh.2007.12.023.**

**218. Grant, A. C., Prus, N., & Nakhutina, L. (2013). Factors affecting quality of life in epilepsy in a multi-ethnic urban population. *Epilepsy Behav, 27*(2), 283-285, doi:10.1016/j.yebeh.2013.01.031.**

**219. Hamid, H., Kasasbeh, A. S., Suleiman, M. J., Cong, X., Liu, H., Mohiuddin, S., et al. (2013). Neuropsychiatric symptoms, seizure severity, employment, and quality of life of Jordanians with epilepsy. *Epilepsy Behav, 27*(1), 272-275, doi:10.1016/j.yebeh.2013.01.013.**

**220. Viteva, E. (2013). Impact of stigma on the quality of life of patients with refractory epilepsy. *Seizure, 22*(1), 64-69, doi:10.1016/j.seizure.2012.10.010.**

**221. Suurmeijer, T. P., Reuvekamp, M. F., & Aldenkamp, B. P. (2001). Social functioning, psychological functioning, and quality of life in epilepsy. *Epilepsia, 42*(9), 1160-1168.**

**222. McLaughlin, D. P., Pachana, N. A., & McFarland, K. (2008). Stigma, seizure frequency and quality of life: the impact of epilepsy in late adulthood. *Seizure, 17*(3), 281-287, doi:10.1016/j.seizure.2007.09.001.**

**223. Whatley, A. D., DiIorio, C. K., & Yeager, K. (2010). Examining the relationships of depressive symptoms, stigma, social support and regimen-specific support on quality of life in adult patients with epilepsy. *Health Educ Res, 25*(4), 575-584, doi:10.1093/her/cyq001.**

**224. Abetz, L., Jacoby, A., Baker, G. A., & McNulty, P. (2000). Patient-based assessments of quality of life in newly diagnosed epilepsy patients: validation of the NEWQOL. *Epilepsia, 41*(9), 1119-1128.**

**225. Kwon, O. Y., & Park, S. P. (2013). Frequency of affective symptoms and their psychosocial impact in Korean people with epilepsy: a survey at two tertiary care hospitals. *Epilepsy Behav, 26*(1), 51-56, doi:10.1016/j.yebeh.2012.10.020.**

**226. Ridsdale, L., Robins, D., Fitzgerald, A., Jeffery, S., & McGee, L. (1996). Epilepsy in general practice: patients' psychological symptoms and their perception of stigma. *Br J Gen Pract, 46*(407), 365-366.**

**227. Adewuya, A. O., & Ola, B. A. (2005). Prevalence of and risk factors for anxiety and depressive disorders in Nigerian adolescents with epilepsy. *Epilepsy Behav, 6*(3), 342-347, doi:S1525-5050(04)00409-3 [pii]10.1016/j.yebeh.2004.12.011.**

**228. Reisinger, E. L., & DiIorio, C. (2009). Individual, seizure-related, and psychosocial predictors of depressive symptoms among people with epilepsy over six months. *Epilepsy Behav, 15*(2), 196-201, doi:S1525-5050(09)00156-5 [pii]10.1016/j.yebeh.2009.03.012.**

**229. Leaffer, E. B., Jacoby, A., Benn, E., Hauser, W. A., Shih, T., Dayan, P., et al. (2011). Associates of stigma in an incident epilepsy population from northern Manhattan, New York City. *Epilepsy & Behavior, 21*(1), 60-64, doi:S1525-5050(11)00110-7 [pii]10.1016/j.yebeh.2011.03.007.**

**230. Viteva, E. (2012). Stigmatization of patients with epilepsy: a review of the current problem and assessment of the perceived stigma in Bulgarian patients. *Epilepsy Behav, 25*(2), 239-243, doi:10.1016/j.yebeh.2012.07.018.**

**231. Buck, D., Jacoby, A., Baker, G. A., & Chadwick, D. W. (1997). Factors influencing compliance with antiepileptic drug regimes. *Seizure, 6*(2), 87-93.**

**232. Austin, J. K., & Huberty, T. J. (1993). Development of the Child Attitude Toward Illness Scale. *J Pediatr Psychol, 18*(4), 467-480.**

**233. Fernandes, P. T., Salgado, P. C., Noronha, A. L., Sander, J. W., & Li, L. M. (2007). Stigma Scale of Epilepsy: validation process. *Arq Neuropsiquiatr, 65 Suppl 1*, 35-42, doi:S0004-282X2007000700006 [pii].**

**234. Prus, N., & Grant, A. C. (2010). Patient beliefs about epilepsy and brain surgery in a multicultural urban population. *Epilepsy Behav, 17*(1), 46-49, doi:10.1016/j.yebeh.2009.09.022.**

**235. Forsgren, L., Ghanean, H., Jacobsson, L., & Richter, J. (2013). On the experience of stigma by persons with epilepsy in Sweden and Iran--a comparative study. *Seizure, 22*(9), 748-751, doi:10.1016/j.seizure.2013.05.016.**

**236. Hyman, M. D. (1971). The stigma of stroke. Its effects on performance during and after rehabilitation. *Geriatrics, 26*(5), 132-141.**

**237. Mulhern, B., Rowen, D., Jacoby, A., Marson, T., Snape, D., Hughes, D., et al. (2012). The development of a QALY measure for epilepsy: NEWQOL-6D. *Epilepsy Behav, 24*(1), 36-43, doi:10.1016/j.yebeh.2012.02.025.**

**238. Link, B. G., & Cullen, F. T. (1983). Reconsidering the social rejection of ex-mental patients: levels of attitudinal response. *Am J Community Psychol, 11*(3), 261-273.**

**239. Bruno, E., Bartoloni, A., Sofia, V., Rafael, F., Magnelli, D., Padilla, S., et al. (2012). Epilepsy-associated stigma in Bolivia: a community-based study among the Guarani**

**population: an International League Against Epilepsy/International Bureau for Epilepsy/World Health Organization Global Campaign Against Epilepsy Regional Project. *Epilepsy Behav, 25*(1), 131-136, doi:10.1016/j.yebeh.2012.07.011.**

**240. Mbuba, C. K., Abubakar, A., Odermatt, P., Newton, C. R., & Carter, J. A. (2012). Development and validation of the Kilifi Stigma Scale for Epilepsy in Kenya. *Epilepsy Behav, 24*(1), 81-85, doi:10.1016/j.yebeh.2012.02.019.**

**241. Elafros, M. A., Sakubita-Simasiku, C., Atadzhanov, M., Haworth, A., Chomba, E., & Birbeck, G. L. (2013). Stigma and psychiatric morbidity among mothers of children with epilepsy in Zambia. *Int Health, 5*(4), 288-294, doi:10.1093/inthealth/iht028.**

**242. Henkel, K., Brown, K., & Kalichman, S. (2008). AIDS-Related Stigma in Individuals With Other Stigmatized Identities in the USA: A Review of Layered Stigmas. *Social and Personality Psychology Compass, 2*(4), 1586-1599.**

**243. Chan, K. Y., Stoove, M. A., Sringernyuang, L., & Reidpath, D. D. (2008). Stigmatization of AIDS patients: disentangling Thai nursing students' attitudes towards HIV/AIDS, drug use, and commercial sex. *AIDS Behav, 12*(1), 146-157, doi:10.1007/s10461-007-9222-y.**

**244. Grossman, A. H. (1991). Gay men and HIV/AIDS: understanding the double stigma. *J Assoc Nurses AIDS Care, 2*(4), 28-32.**

**245. Deribew, A., Hailemichael, Y., Tesfaye, M., Desalegn, D., Wogi, A., & Daba, S. (2010). The synergy between TB and HIV co-infection on perceived stigma in Ethiopia. *BMC Res Notes, 3*, 249, doi:10.1186/1756-0500-3-249.**

**246. Bond, V., & Nyblade, L. (2006). The importance of addressing the unfolding TB-HIV stigma in high HIV prevalence settings. *Journal of Community & Applied Social Psychology, 16*(6), 452-461, doi:10.1002/casp.893.**

**247. Walkup, J., Cramer, L. J., & Yeras, J. (2004). How is stigmatization affected by the "layering" of stigmatized conditions, such as serious mental illness and HIV? *Psychol Rep, 95*(3 Pt 1), 771-779.**

**248. Molina, Y., Choi, S. W., Cella, D., & Rao, D. (2013). The stigma scale for chronic illnesses 8-item version (SSCI-8): development, validation and use across neurological conditions. *Int J Behav Med, 20*(3), 450-460, doi:10.1007/s12529-012-9243-4.**

**249. Rao, D., Choi, S. W., Victorson, D., Bode, R., Peterman, A., Heinemann, A., et al. (2009). Measuring stigma across neurological conditions: the development of the stigma scale for chronic illness (SSCI). *Qual Life Res, 18*(5), 585-595, doi:10.1007/s11136-009-9475-1.**

**250. Gallo, R. C. (2006). A reflection on HIV/AIDS research after 25 years. *Retrovirology, 3*, 72, doi:10.1186/1742-4690-3-72.**

**251. Administration, F. a. D. (2013). Approved Drug Products with Therapeutic Equivalence Evaluations. In U. S. D. o. H. A. H. Services (Ed.), (33 ed.).**

**252. Creagh-Kirk, T., Doi, P., Andrews, E., Nusinoff-Lehrman, S., Tilson, H., Hoth, D., et al. (1988). Survival experience among patients with AIDS receiving zidovudine. Follow-up of patients in a compassionate plea program. *JAMA, 260*(20), 3009-3015.**

**253. Yarchoan, R., Pluda, J. M., Perno, C. F., Mitsuya, H., Thomas, R. V., Wyvill, K. M., et al. (1990). Initial clinical experience with dideoxynucleosides as single agents and in combination therapy. *Ann N Y Acad Sci, 616*, 328-343.**

**254. Committee, I. T. I. C.-o., Yeni, P., Cooper, D. A., Aboulker, J. P., Babiker, A. G., Carey, D., et al. (2006). Virological and immunological outcomes at 3 years after starting antiretroviral therapy with regimens containing non-nucleoside reverse transcriptase inhibitor, protease inhibitor, or both in INITIO: open-label randomised trial. *Lancet, 368*(9532), 287-298, doi:10.1016/S0140-6736(06)69074-0.**

**255. WHO (2013). Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection. *A Public Health Approach*. Geneva.**

**256. Kanters, S., Mills, E. J., Thorlund, K., Bucher, H. C., & Ioannidis, J. P. (2014). Antiretroviral therapy for initial human immunodeficiency virus/AIDS treatment: critical appraisal of the evidence from over 100 randomized trials and 400 systematic reviews and meta-analyses. *Clin Microbiol Infect, 20*(2), 114-122, doi:10.1111/1469-0691.12475.**

**257. Este, J. A., & Cihlar, T. (2010). Current status and challenges of antiretroviral research and therapy. *Antiviral Res, 85*(1), 25-33, doi:10.1016/j.antiviral.2009.10.007.**

**258. Cohen, M. S., Chen, Y. Q., McCauley, M., Gamble, T., Hosseinipour, M. C., Kumarasamy, N., et al. (2011). Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med, 365*(6), 493-505, doi:10.1056/NEJMoa1105243.**

**259. Wang, H., Zhou, J., He, G., Luo, Y., Li, X., Yang, A., et al. (2009). Consistent ART adherence is associated with improved quality of Life, CD4 counts, and reduced hospital costs in central China. *AIDS Res Hum Retroviruses, 25*(8), 757-763, doi:10.1089/aid.2008.0173.**

**260. Bangsberg, D. R., Perry, S., Charlebois, E. D., Clark, R. A., Roberston, M., Zolopa, A. R., et al. (2001). Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS, 15*(9), 1181-1183.**

**261. McNabb, J., Ross, J. W., Abriola, K., Turley, C., Nightingale, C. H., & Nicolau, D. P. (2001). Adherence to highly active antiretroviral therapy predicts virologic outcome at an inner-city human immunodeficiency virus clinic. *Clin Infect Dis, 33*(5), 700-705, doi:10.1086/322590.**

**262. Gross, R., Yip, B., Lo Re, V., 3rd, Wood, E., Alexander, C. S., Harrigan, P. R., et al. (2006). A simple, dynamic measure of antiretroviral therapy adherence predicts failure to maintain HIV-1 suppression. *J Infect Dis, 194*(8), 1108-1114, doi:10.1086/507680.**

**263. Gross, R., Bilker, W. B., Friedman, H. M., & Strom, B. L. (2001). Effect of adherence to newly initiated antiretroviral therapy on plasma viral load. *AIDS, 15*(16), 2109-2117.**

**264. Catz, S. L., Kelly, J. A., Bogart, L. M., Benotsch, E. G., & McAuliffe, T. L. (2000). Patterns, correlates, and barriers to medication adherence among persons prescribed new treatments for HIV disease. *Health Psychol, 19*(2), 124-133.**

**265. Blanch, J., Martinez, E., Rousaud, A., Blanco, J. L., Garcia-Viejo, M. A., Peri, J. M., et al. (2001). Preliminary data of a prospective study on neuropsychiatric side effects after initiation of efavirenz. *J Acquir Immune Defic Syndr, 27*(4), 336-343.**

**266. Trotta, M. P., Ammassari, A., Melzi, S., Zaccarelli, M., Ladisa, N., Sighinolfi, L., et al. (2002). Treatment-related factors and highly active antiretroviral therapy adherence. *J Acquir Immune Defic Syndr, 31 Suppl 3*, S128-131.**

**267. Lucas, G. M., Wu, A. W., & Cheever, L. W. (2004). Adherence to antiretroviral therapy: an update of current concepts. *Curr HIV/AIDS Rep, 1*(4), 172-180.**

**268. Monforte, A., Lepri, A., Rezza, G., Pezzotti, P., Antinori, A., Philips, A., et al. (2000). Insights into the reason for discontiuation of the first highly active antiretroviral**

**therapy (HAART) regimen in a cohort of antiretroviral naive patients. *AIDS Alert, 14*(5), 499-507.**

**269. GlaxoSmithKline (2008). Retrovir (zidovudine) Tablets, Capsules, and Syrup. In GlaxoSmithKline (Ed.).**

**270. Palacios, R., Santos, J., Camino, X., Arazo, P., Torres Perea, R., Echevarria, S., et al. (2005). Treatment-Limiting Toxicities Associated with Nucleoside Analogue Reverse Transcriptase Inhibitor Therapy: A Prosepective, Observational Study. *Current Therapeutic Research, 66*(2), 117-129.**

**271. DeJesus, E., Herrera, G., Teofilo, E., Gerstoft, J., Buendia, C. B., Brand, J. D., et al. (2004). Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. *Clin Infect Dis, 39*(7), 1038-1046, doi:10.1086/424009.**

**272. Feleke, Y., Fekade, D., & Mezegebu, Y. (2012). Prevalence of highly active antiretroviral therapy associated metabolic abnormalities and lipodystrophy in HIV infected patients. *Ethiop Med J, 50*(3), 221-230.**

**273. Carr, A., & Cooper, D. A. (2000). Adverse effects of antiretroviral therapy. *Lancet, 356*(9239), 1423-1430, doi:10.1016/S0140-6736(00)02854-3.**

**274. Hawkins, T. (2010). Understanding and managing the adverse effects of antiretroviral therapy. *Antiviral Res, 85*(1), 201-209, doi:10.1016/j.antiviral.2009.10.016.**

**275. Squibb, B.-M. (2012). Videx (didanosine, USP) capsules. In B.-M. Squibb (Ed.).**

**276. Calmy, A., Hirschel, B., Cooper, D. A., & Carr, A. (2009). A new era of antiretroviral drug toxicity. *Antivir Ther, 14*(2), 165-179.**

**277. Squibb, B.-M. (2012). Zerit (stavudine) Capsules. In B.-M. Squibb (Ed.).**

**278. Phan, V., Thai, S., Choun, K., Lynen, L., & van Griensven, J. (2012). Incidence of treatment-limiting toxicity with stavudine-based antiretroviral therapy in Cambodia: a retrospective cohort study. *PLoS One, 7*(1), e30647, doi:10.1371/journal.pone.0030647.**

**279. Fellay, J., Boubaker, K., Ledergerber, B., Bernasconi, E., Furrer, H., Battegay, M., et al. (2001). Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV Cohort Study. *Lancet, 358*(9290), 1322-1327.**

**280. GlaxoSmithKline (2011). Epivir (lamivudine) Tablets and Oral Solution. In GlaxoSmithKline (Ed.).**

**281. GlaxoSmithKline (2002). Epivir Tablets (Lamivudine tablets). In GlaxoSmithKline (Ed.).**

**282. Kanmaz, T. J., & Lee, N. J. (2000). Significant Toxicities Associated with Antiretroviral Therapy. *Journal of Pharmacy Practice, 13*(6), 457-474, doi:10.1106/2uu8-8jjd-uhru-c14r.**

**283. GlaxosSmithKline (2012). Ziagen (abacavir sulfate) Tablets, for oral use. In GlaxosSmithKline (Ed.).**

**284. Sciences, G. (2013). Viread (tenofovir disoproxil fumarate) tablets, for oral use. In G. Sciences (Ed.).**

**285. Nishijima, T., Yazaki, H., Hinoshita, F., Tasato, D., Hoshimoto, K., Teruya, K., et al. (2012). Drug-induced acute interstitial nephritis mimicking acute tubular necrosis after initiation of tenofovir-containing antiretroviral therapy in patient with HIV-1 infection. *Intern Med, 51*(17), 2469-2471.**

**286. Sciences, G. (2012). Emtriva (emtricitabine) capsule for oral use.**

**287. Moyle, G. (2000). Clinical manifestations and management of antiretroviral nucleoside analog-related mitochondrial toxicity. *Clin Ther, 22*(8), 911-936; discussion 898, doi:10.1016/S0149-2918(00)80064-8.**

**288. Boerhringer Ingelheim Pharmaceuticals, I. (2012). Viramune (nevirapine) Tablets, for oral use. In I. Boerhringer Ingelheim Pharmaceuticals (Ed.).**

**289. Shubber, Z., Calmy, A., Andrieux-Meyer, I., Vitoria, M., Renaud-Thery, F., Shaffer, N., et al. (2013). Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy: a systematic review and meta-analysis. *AIDS, 27*(9), 1403-1412, doi:10.1097/QAD.0b013e32835f1db0.**

**290. Martinez, E., Blanco, J. L., Arnaiz, J. A., Perez-Cuevas, J. B., Mocroft, A., Cruceta, A., et al. (2001). Hepatotoxicity in HIV-1-infected patients receiving nevirapine-containing antiretroviral therapy.** ***AIDS, 15*****(10), 1261-1268.**

**291. Squibb, B.-M. (2013). Sustiva (efavirenz) capsules for oral use. In B.-M. Squibb (Ed.).**

**292. AbbVie (2013). Keletra (lopinavir/ritonavir) capsules. In AbbVie (Ed.).**

**293. Ortiz, R., Dejesus, E., Khanlou, H., Voronin, E., van Lunzen, J., Andrade-Villanueva, J., et al. (2008). Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48.** ***AIDS, 22*****(12), 1389-1397, doi:10.1097/QAD.0b013e32830285fb.**

**294. Molina, J. M., Andrade-Villanueva, J., Echevarria, J., Chetchotisakd, P., Corral, J., David, N., et al. (2008). Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study.** ***Lancet, 372*****(9639), 646-655, doi:10.1016/S0140-6736(08)61081-8.**

**295. Squibb, B.-M. (2013). Reyataz (atazanir sulfate) Capsules. In B.-M. Squibb (Ed.).**

**296. Tapsfield, J., Mathews, T., Lungu, M., & Van Oosterhout, J. J. (2011). Underreporting of side effects of standard first-line ART in the routine setting in Blantyre, Malawi.** ***Malawi Med J, 23*****(4), 115-117.**

**297. WHO (2013). HIV/AIDS Programme: surveillance of antiretroviral drug toxicity within antiretroviral treatment programs.** ***Technical Brief: Surveillance of Antiretroviral Thoxicity*****.**

**298. Perucca, E. (2005). An introduction to antiepileptic drugs.** ***Epilepsia, 46 Suppl 4*****, 31-37.**

**299. Potschka, H. (2013). Pharmacological treatment strategies: Mechanisms of antiepileptic drugs.** ***Epileptology, 1*****(1), 31-37, doi:10.1016/j.epilep.2012.11.004.**

**300. WHO (2013). Standard antiepileptic drugs (phenobarbital, phenytoin, carbamazepine, valproic acid) for management of convulsive epilepsy in adults and children** ***WHO Mental Health Gap Action Programme (mhGAP): mhGAP Evidence Resource Center, Epilepsy and Seizures*****. Geneva: World Health Organization.**

**301. Mintzer, S., & Mattson, R. T. (2009). Should enzyme-inducing antiepileptic drugs be considered first-line agents? *Epilepsia, 50 Suppl 8*, 42-50, doi:10.1111/j.1528-1167.2009.02235.x.**

**302. Neligan, A., & Sander, J. W. (2013). The treatment gap in epilepsy: A global perspective. *Epileptology, 1*(1), 28-30, doi:10.1016/j.epilep.2012.11.002.**

**303. Chomba, E. N., Haworth, A., Mbewe, E., Atadzhanov, M., Ndubani, P., Kansembe, H., et al. (2010). The current availability of antiepileptic drugs in Zambia: implications for the ILAE/WHO "out of the shadows" campaign. *Am J Trop Med Hyg, 83*(3), 571-574, doi:10.4269/ajtmh.2010.10-0100.**

**304. Jones, R. M., Butler, J. A., Thomas, V. A., Peveler, R. C., & Prevett, M. (2006). Adherence to treatment in patients with epilepsy: associations with seizure control and illness beliefs. *Seizure, 15*(7), 504-508, doi:10.1016/j.seizure.2006.06.003.**

**305. Cramer, J. A., Glassman, M., & Rienzi, V. (2002). The relationship between poor medication compliance and seizures. *Epilepsy Behav, 3*(4), 338-342.**

**306. Cloyd, J. C., & Remmel, R. P. (2000). Antiepileptic drug pharmacokinetics and interactions: impact on treatment of epilepsy. *Pharmacotherapy, 20*(8 Pt 2), 139S-151S.**

**307. Iivanainen, M., & Savolainen, H. (1983). Side effects of phenobarbital and phenytoin during long-term treatment of epilepsy. *Acta Neurol Scand Suppl, 97*, 49-67.**

**308. Bekele, G., Abebe, Y., & T'Haimanot, R. (1990). Plasma level distribution, effect and toxicity of antiepileptic drugs among Ethiopian epileptics. *Ethiop Med J, 28*(1), 23-30.**

**309. Medicines and healthcare Products Regulatory Agency, U. (2011). Phenobarbital 30mg and 60mg Tablets.**

**310. Dreifuss, F. E., & Langer, D. H. (1988). Side effects of valproate. *Am J Med, 84*(1A), 34-41.**

**311. Banu, S. H., Jahan, M., Koli, U. K., Ferdousi, S., Khan, N. Z., & Neville, B. (2007). Side effects of phenobarbital and carbamazepine in childhood epilepsy: randomised controlled trial. *BMJ, 334*(7605), 1207, doi:10.1136/bmj.39022.436389.BE.**

**312. Novartis (2013). Tegretol (Carbamazepine USP). In Novartis (Ed.).**

**313. Neppe, V. M., Tucker, G. J., & Wilensky, A. J. (1988). Fundamentals of carbamazepine use in neuropsychiatry. *J Clin Psychiatry, 49 Suppl*, 4-6.**

**314. Gillham, R. A., Williams, N., Wiedmann, K. D., Butler, E., Larkin, J. G., & Brodie, M. J. (1990). Cognitive function in adult epileptic patients established on anticonvulsant monotherapy. *Epilepsy Res, 7*(3), 219-225.**

**315. Rittmannsberger, H., & Leblhuber, F. (1992). Asterixis induced by carbamazepine therapy. *Biol Psychiatry, 32*(4), 364-368.**

**316. Mattson, R. H., Cramer, J. A., Collins, J. F., Smith, D. B., Delgado-Escueta, A. V., Browne, T. R., et al. (1985). Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. *N Engl J Med, 313*(3), 145-151, doi:10.1056/NEJM198507183130303.**

**317. Phzer (2012). Dilantin (extended phenytoin sodium capsuls, USP).**

**318. AbbVie (2013). Depacon (valproate sodium) for intravenous injection. In AbbVie (Ed.).**

**319. Gunes, A., Bilir, E., Zengil, H., Babaoglu, M. O., Bozkurt, A., & Yasar, U. (2007). Inhibitory effect of valproic acid on cytochrome P450 2C9 activity in epilepsy patients. *Basic Clin Pharmacol Toxicol, 100*(6), 383-386, doi:10.1111/j.1742-7843.2007.00061.x.**

**320. Zeber, J. E., Copeland, L. A., & Pugh, M. J. (2010). Variation in antiepileptic drug adherence among older patients with new-onset epilepsy. *Ann Pharmacother, 44*(12), 1896-1904, doi:10.1345/aph.1P385.**

**321. Gaitatzis, A., & Sander, J. W. (2013). The long-term safety of antiepileptic drugs. *CNS Drugs, 27*(6), 435-455, doi:10.1007/s40263-013-0063-0.**

**322. Paschal, A. M., Rush, S. E., & Sadler, T. (2013). Factors associated with medication adherence in patients with epilepsy and recommendations for improvement. *Epilepsy Behav*, doi:10.1016/j.yebeh.2013.10.002.**

**323. Andersen, E. B., Philbert, A., & Klee, J. G. (1983). Carbamazepine monotherapy in epileptic out-patients. *Acta Neurol Scand Suppl, 94*, 29-34.**

**324. Herranz, J. L., Armijo, J. A., & Arteaga, R. (1988). Clinical side effects of phenobarbital, primidone, phenytoin, carbamazepine, and valproate during monotherapy in children. *Epilepsia, 29*(6), 794-804.**

**325. Kwan, P., & Brodie, M. J. (2001). Effectiveness of first antiepileptic drug. *Epilepsia, 42*(10), 1255-1260.**

**326. Chung, S., Wang, N., & Hank, N. (2007). Comparative retention rates and long-term tolerability of new antiepileptic drugs. *Seizure, 16*(4), 296-304, doi:10.1016/j.seizure.2007.01.004.**

**327. Birbeck, G. L. (2010). Epilepsy Care in Developing Countries: Part II of II. *Epilepsy Curr, 10*(5), 105-110, doi:10.1111/j.1535-7511.2010.01372.x.**

**328. Bruno, E., Nimaga, K., Foba, I., Vignoles, P., Genton, P., Doumbo, O., et al. (2012). Results of an action-research on epilepsy in rural Mali. *PLoS One, 7*(8), e44469, doi:10.1371/journal.pone.0044469.**

**329. Kwan, P., Wang, W., Wu, J., Li, S., Yang, H., Ding, D., et al. (2013). Long-term outcome of phenobarbital treatment for epilepsy in rural China: a prospective cohort study. *Epilepsia, 54*(3), 537-542, doi:10.1111/epi.12022.**

**330. Nimaga, K., Desplats, D., Doumbo, O., & Farnarier, G. (2002). Treatment with phenobarbital and monitoring of epileptic patients in rural Mali. *Bull World Health Organ, 80*(7), 532-537.**

**331. Mani, K. S., Rangan, G., Srinivas, H. V., Srindharan, V. S., & Subbakrishna, D. K. (2001). Epilepsy control with phenobarbital or phenytoin in rural south India: the Yelandur study. *Lancet, 357*(9265), 1316-1320.**

**332. Ding, D., Zhang, Q., Zhou, D., Lin, W., Wu, Q., Sun, J., et al. (2012). Cognitive and mood effects of phenobarbital treatment in people with epilepsy in rural China: a prospective study. *J Neurol Neurosurg Psychiatry, 83*(12), 1139-1144, doi:10.1136/jnnp-2012-303042.**

**333. Goodacre, L. J., & Goodacre, J. A. (2004). Factors influencing the beliefs of patients with rheumatoid arthritis regarding disease-modifying medication. *Rheumatology (Oxford), 43*(5), 583-586, doi:10.1093/rheumatology/keh116.**

**334. Horne, R. L. (1999). Patients' beliefs about treatment: the hidden determinant of treatment outcome? *J Psychosom Res, 47*(6), 491-495.**

**335. Gao, X., Nau, D. P., Rosenbluth, S. A., Scott, V., & Woodward, C. (2000). The relationship of disease severity, health beliefs and medication adherence among HIV patients. *AIDS Care, 12*(4), 387-398, doi:10.1080/09540120050123783.**

**336. Brodie, M. J., Mintzer, S., Pack, A. M., Gidal, B. E., Vecht, C. J., & Schmidt, D. (2013). Enzyme induction with antiepileptic drugs: cause for concern? *Epilepsia, 54*(1), 11-27, doi:10.1111/j.1528-1167.2012.03671.x.**

**337. Nebert, D. W., & Russell, D. W. (2002). Clinical importance of the cytochromes P450. *The Lancet, 360*(9340), 1155-1162, doi:10.1016/s0140-6736(02)11203-7.**

**338. Anderson, G. D. (2004). Pharmacogenetics and enzyme induction/inhibition properties of antiepileptic drugs. *Neurology, 63*(10 Suppl 4), S3-8, doi:63/10_suppl_4/S3 [pii].**

**339. Magnusson, M. O., Dahl, M. L., Cederberg, J., Karlsson, M. O., & Sandstrom, R. (2008). Pharmacodynamics of carbamazepine-mediated induction of CYP3A4, CYP1A2, and Pgp as assessed by probe substrates midazolam, caffeine, and digoxin. *Clin Pharmacol Ther, 84*(1), 52-62, doi:10.1038/sj.clpt.6100431.**

**340. Imai, H., Kotegawa, T., Tsutsumi, K., Morimoto, T., Eshima, N., Nakano, S., et al. (2008). The recovery time-course of CYP3A after induction by St John's wort administration. *Br J Clin Pharmacol, 65*(5), 701-707, doi:10.1111/j.1365-2125.2008.03120.x.**

**341. Punyawudho, B., Cloyd, J. C., Leppik, I. E., Ramsay, R. E., Marino, S. E., Pennell, P. B., et al. (2009). Characterization of the time course of carbamazepine deinduction by an enzyme turnover model. *Clin Pharmacokinet, 48*(5), 313-320, doi:10.2165/00003088-200948050-00003.**

**342. Bourgeois, B. F. (1988). Anticonvulsant potency and neurotoxicity of valproate alone and in combination with carbamazepine or phenobarbital. *Clin Neuropharmacol, 11*(4), 348-359.**

**343. Christiansen, J., & Dam, M. (1973). Influence of phenobarbital and diphenylhydantoin on plasma carbamazepine levels in patients with epilepsy. *Acta Neurol Scand, 49*(4), 543-546.**

**344. Kemper, B. (1998). Regulation of cytochrome P450 gene transcription by phenobarbital. *Prog Nucleic Acid Res Mol Biol, 61*, 23-64.**

**345. Michaud, V., Ogburn, E., Thong, N., Aregbe, A. O., Quigg, T. C., Flockhart, D. A., et al. (2012). Induction of CYP2C19 and CYP3A activity following repeated administration of efavirenz in healthy volunteers. *Clin Pharmacol Ther, 91*(3), 475-482, doi:10.1038/clpt.2011.249.**

**346. Ngaimisi, E., Mugusi, S., Minzi, O. M., Sasi, P., Riedel, K. D., Suda, A., et al. (2010). Long-term efavirenz autoinduction and its effect on plasma exposure in HIV patients. *Clin Pharmacol Ther, 88*(5), 676-684, doi:10.1038/clpt.2010.172.**

**347. Cvetkovic, R. S., & Goa, K. L. (2003). Lopinavir/ritonavir: a review of its use in the management of HIV infection. *Drugs, 63*(8), 769-802.**

**348. Lim, M. L., Min, S. S., Eron, J. J., Bertz, R. J., Robinson, M., Gaedigk, A., et al. (2004). Coadministration of lopinavir/ritonavir and phenytoin results in two-way drug interaction through cytochrome P-450 induction. *J Acquir Immune Defic Syndr, 36*(5), 1034-1040.**

**349. Wyen, C., Fuhr, U., Frank, D., Aarnoutse, R. E., Klaassen, T., Lazar, A., et al. (2008). Effect of an antiretroviral regimen containing ritonavir boosted lopinavir on intestinal and hepatic CYP3A, CYP2D6 and P-glycoprotein in HIV-infected patients. *Clin Pharmacol Ther, 84*(1), 75-82, doi:10.1038/sj.clpt.6100452.**

**350. Hariparsad, N., Nallani, S. C., Sane, R. S., Buckley, D. J., Buckley, A. R., & Desai, P. B. (2004). Induction of CYP3A4 by efavirenz in primary human hepatocytes: comparison with rifampin and phenobarbital. *J Clin Pharmacol, 44*(11), 1273-1281, doi:44/11/1273 [pii]10.1177/0091270004269142.**

**351. DiCenzo, R., Peterson, D., Cruttenden, K., Morse, G., Riggs, G., Gelbard, H., et al. (2004). Effects of valproic acid coadministration on plasma efavirenz and lopinavir concentrations in human immunodeficiency virus-infected adults. *Antimicrob Agents Chemother, 48*(11), 4328-4331, doi:10.1128/AAC.48.11.4328-4331.2004.**

**352. L'homme, R., Dijkema, T., van der Ven, A., & Burger, D. (2006). Brief Report: Enzyme Inducers Reduce Elimination Half-Life After a Single Dose of Nevirapine in Healthy Women. *J Acquir Immune Defic Syndr, 43*(2), 193-196.**

**353. Birbeck, G. L., French, J. A., Perucca, E., Simpson, D. M., Fraimow, H., George, J. M., et al. (2012). Evidence-based guideline: Antiepileptic drug selection for people with HIV/AIDS: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Ad Hoc Task Force of the Commission on Therapeutic Strategies of the International League Against Epilepsy. *Neurology, 78*(2), 139-145, doi:10.1212/WNL.0b013e31823efcf8.**

**354. Jetter, A., Fatkenheuer, G., Frank, D., Klaassen, T., Seeringer, A., Doroshyenko, O., et al. (2010). Do activities of cytochrome P450 (CYP)3A, CYP2D6 and P-glycoprotein differ between healthy volunteers and HIV-infected patients? *Antivir Ther, 15*(7), 975-983, doi:10.3851/IMP1648.**

**355. Okulicz, J. F., Grandits, G. A., French, J. A., Perucca, E., George, J. M., Landrum, M. L., et al. (2012). The impact of enzyme-inducing antiepileptic drugs on antiretroviral drug levels: A case-control study. *Epilepsy Res*, doi:10.1016/j.eplepsyres.2012.07.009.**

**356. Okulicz, J. F., Grandits, G. A., French, J. A., George, J. M., Simpson, D. M., Birbeck, G. L., et al. (2011). Virologic outcomes of HAART with concurrent use of cytochrome P450 enzyme-inducing antiepileptics: a retrospective case control study. *AIDS Res Ther, 8*(1), 18, doi:1742-6405-8-18 [pii]10.1186/1742-6405-8-18.**

**357. Birbeck, G., Chomba, E., Atadzhanov, M., Mbewe, E., & Haworth, A. (2007). The social and economic impact of epilepsy in Zambia: a cross-sectional study. *Lancet Neurology, 6*(1), 39-44, doi:S1474-4422(06)70629-9 [pii]10.1016/S1474-4422(06)70629-9.**

**358. Wright, E., Brew, B. J., Lal, L., Ali, S. T., Arayawichanont, A., Imran, D., et al. (2008). Response to Birbeck et al. *Epilepsia, 49*(3), 541-543, doi:10.1111/j.1528-1167.2007.01529_5.x.**

**359. Gomez-Arias, B., Crail-Melendez, D., Lopez-Zapata, R., & Martinez-Juarez, I. E. (2012). Severity of anxiety and depression are related to a higher perception of adverse effects of antiepileptic drugs. *Seizure, 21*(8), 588-594, doi:10.1016/j.seizure.2012.06.003.**

**360. Birbeck, G., Chomba, E., Atadzhanov, M., Mbewe, E., & Haworth, A. (2007). The social and economic impact of epilepsy in Zambia: a cross-sectional study. *Lancet Neurol, 6*(1), 39-44, doi:S1474-4422(06)70629-9 [pii]10.1016/S1474-4422(06)70629-9.**

**361. Chomba, E., Haworth, A., Atadzhanov, M., Mbewe, E., & Birbeck, G. L. (2008). The socioeconomic status of children with epilepsy in Zambia: implications for long-term health and well-being. *Epilepsy Behav, 13*(4), 620-623, doi:S1525-5050(08)00192-3 [pii]10.1016/j.yebeh.2008.06.008.**

**362. de Kinderen, R. J., Evers, S. M., Rinkens, R., Postulart, D., Vader, C. I., Majoie, M. H., et al. (2013). Side-effects of antiepileptic drugs: The economic burden. *Seizure*, doi:10.1016/j.seizure.2013.11.009.**

**363. UNAIDS (2009). AIDS Epidemic Update. New York: uNAIDS.**

**364. de Boer, H. M., Mula, M., & Sander, J. W. (2008). The global burden and stigma of epilepsy. *Epilepsy Behav, 12*(4), 540-546, doi:S1525-5050(07)00487-8 [pii]10.1016/j.yebeh.2007.12.019.**

**365. Elafros, M. A., Mulenga, J., Mbewe, E., Haworth, A., Chomba, E., Atadzhanov, M., et al. (2013). Peer support groups as an intervention to decrease epilepsy-associated stigma. *Epilepsy Behav, 27*(1), 188-192, doi:10.1016/j.yebeh.2013.01.005.**

**366. Birbeck, G. (2006). Interventions to reduce epilepsy-associated stigma. *Psychol Health Med, 11*(3), 364-366, doi:N881437G56627N66 [pii]10.1080/13548500600595343.**

**367. Rafael, F., Dubreuil, C. M., Burbaud, F., Tran, D. S., Clement, J. P., Preux, P. M., et al. (2010). Knowledge of epilepsy in the general population based on two French cities: implications for stigma. *Epilepsy Behav, 17*(1), 82-86, doi:10.1016/j.yebeh.2009.10.014.**

**368. Youssef, F. F., Dial, S., Jaggernauth, N., Jagdeo, C. L., Pascall, A., Ramessar, L., et al. (2009). Knowledge of, attitudes toward, and perceptions of epilepsy among college students in Trinidad and Tobago. *Epilepsy Behav, 15*(2), 160-165, doi:10.1016/j.yebeh.2009.01.027.**

**369. Donkor, E. S., & Sandall, J. (2007). The impact of perceived stigma and mediating social factors on infertility-related stress among women seeking infertility treatment in Southern Ghana. *Soc Sci Med, 65*(8), 1683-1694, doi:10.1016/j.socscimed.2007.06.003.**

**370. Herodes, M., Oun, A., Haldre, S., & Kaasik, A. E. (2001). Epilepsy in Estonia: a quality-of-life study. *Epilepsia, 42*(8), 1061-1073.**

**371. Bielen, I., Friedrich, L., Sruk, A., Prvan, M. P., Hajnšek, S., Petelin, Ž., et al. (2013). Factors associated with perceived stigma of epilepsy in Croatia: A study USING the revised epilepsy stigma scale. *Seizure*, doi:10.1016/j.seizure.2013.10.008.**

**372. Embretson, S., & PReise, S. (2000). *Item response theory for psychologists*. New Jersey: Lawrence Erlbaum Associates, Inc, Publishers.**

**373. Cattell, R. (1966). The Scree Test For The Number Of Factors. *Multivariate Behavioral Research, 1*(2), 245-276.**

**374. Reckase, M. (2009). *Multidementional Item Response Theory*. London: Springer.**

**375. Zumbo, B. (2007). Three Generations of DIF Analyses: Considering Where It Has Been, Where It Is Now, and Where It Is Going. *Language Assessment Quarterly, 4*(2), 223-233.**

**376. WHO (2008). mhGAP : Mental Health Gap Action Programme : scaling up care for mental, neurological and substance use disorders. (pp. 44). Geneva: World Health Organization.**

**377. Diiorio, C., McCarty, F., Depadilla, L., Resnicow, K., Holstad, M. M., Yeager, K., et al. (2009). Adherence to antiretroviral medication regimens: a test of a psychosocial model. *AIDS Behav, 13*(1), 10-22, doi:10.1007/s10461-007-9318-4.**

**378. DiIorio, C., Osborne Shafer, P., Letz, R., Henry, T., Schomer, D. L., Yeager, K., et al. (2003). The association of stigma with self-management and perceptions of health care among adults with epilepsy. *Epilepsy Behav, 4*(3), 259-267.**

**379. Sayles, J. N., Wong, M. D., Kinsler, J. J., Martins, D., & Cunningham, W. E. (2009). The association of stigma with self-reported access to medical care and antiretroviral therapy adherence in persons living with HIV/AIDS. *J Gen Intern Med, 24*(10), 1101-1108, doi:10.1007/s11606-009-1068-8.**

**380. Stevelink, S. A. M., Wu, I. C., Voorend, C. G. N., & vn Brakel, W. H. (2012). The Psychometric Assessment of Internalized Stigma Instruments: A Systematic Review. *Stigma Res Action, 2*(2), 100-118.**

**381. Herek, G. M. (1999). AIDS and Stigma. *American Behavioral Scientist, 42*(7), 1106-1116, doi:10.1177/0002764299042007004.**

**382. Hunter, D. J., & Reddy, K. S. (2013). Noncommunicable diseases. *N Engl J Med, 369*(14), 1336-1343, doi:10.1056/NEJMra1109345.**

**383. Dans, A., Ng, N., Varghese, C., Tai, E. S., Firestone, R., & Bonita, R. (2011). The rise of chronic non-communicable diseases in southeast Asia: time for action. *Lancet, 377*(9766), 680-689, doi:10.1016/S0140-6736(10)61506-1.**

**384. Wagner, K. H., & Brath, H. (2012). A global view on the development of non communicable diseases. *Prev Med, 54 Suppl*, S38-41, doi:10.1016/j.ypmed.2011.11.012.**

**385. Magafu, M. G., Moji, K., Igumbor, E. U., Hashizume, M., Mizota, T., Komazawa, O., et al. (2009). Usefulness of highly active antiretroviral therapy on health-related quality of life of adult recipients in Tanzania. *AIDS Patient Care STDS, 23*(7), 563-570, doi:10.1089/apc.2008.0278.**

**386. Nigatu, T. (2012). Integration of HIV and noncommunicable diseases in health care delivery in low- and middle-income countries. *Prev Chronic Dis, 9*, E93.**

**387. Hirschhorn, L. R., Kaaya, S. F., Garrity, P. S., Chopyak, E., & Fawzi, M. C. (2012). Cancer and the 'other' noncommunicable chronic diseases in older people living with HIV/AIDS in resource-limited settings: a challenge to success. *AIDS, 26 Suppl 1*, S65-75, doi:10.1097/QAD.0b013e328355ab72.**

**388. Birbeck, G. L. (2010). Epilepsy care in developing countries: part I of II. *Epilepsy Curr, 10*(4), 75-79, doi:10.1111/j.1535-7511.2010.01362.x.**

**389. Kvalsund, M. P., Haworth, A., Murman, D. L., Velie, E., & Birbeck, G. L. (2009). Closing gaps in antiretroviral therapy access: human immunodeficiency virus-associated dementia screening instruments for non-physician healthcare workers. *Am J Trop Med Hyg, 80*(6), 1054-1059, doi:80/6/1054 [pii].**

**390. Holguin, A., Banda, M., Willen, E. J., Malama, C., Chiyenu, K. O., Mudenda, V. C., et al. (2011). HIV-1 effects on neuropsychological performance in a resource-limited country, Zambia. *AIDS Behav, 15*(8), 1895-1901, doi:10.1007/s10461-011-9988-9.**

**391. Patel, V., Simunyu, E., Gwanzura, F., Lewis, G., & Mann, A. (1997). The Shona Symptom Questionnaire: the development of an indigenous measure of common mental disorders in Harare.** ***Acta Psychiatrica Scandinavica, 95*****(6), 469-475.**

**392. Jelsma, J., Mhundwa, K., De Weerdt, W., De Cock, P., Chimera, J., & Chivaura, V. (2001). The reliability of the Shona version of the EQ-5D.** ***Cent Afr J Med, 47*****(1), 8-13.**

**393. Li, S., Wu, J., Wang, W., Jacoby, A., de Boer, H., & Sander, J. W. (2010). Stigma and epilepsy: the Chinese perspective.** ***Epilepsy Behav, 17*****(2), 242-245, doi:S1525-5050(09)00693-3 [pii]10.1016/j.yebeh.2009.12.015.**

**394. Fernandes, P. T., Noronha, A. L., Sander, J. W., & Li, L. M. (2008). Stigma scale of epilepsy: the perception of epilepsy stigma in different cities in Brazil.** ***Arq Neuropsiquiatr, 66*****(3A), 471-476, doi:S0004-282X2008000400006 [pii].**

**395. Birbeck, G. L., Chomba, E., Atadzhanov, M., Mbewe, E., & Haworth, A. (2008). Women's experiences living with epilepsy in Zambia.** ***American Journal of Tropical Medicine and Hygiene, 79*****(2), 168-172, doi:79/2/168 [pii].**

**396. Yasiry, Z., & Shorvon, S. D. (2012). How phenobarbital revolutionized epilepsy therapy: the story of phenobarbital therapy in epilepsy in the last 100 years.** ***Epilepsia, 53 Suppl 8*****, 26-39, doi:10.1111/epi.12026.**

**397. French, J. A., Kanner, A. M., Bautista, J., Abou-Khalil, B., Browne, T., Harden, C. L., et al. (2004). Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society.** ***Neurology, 62*****(8), 1252-1260.**

**398. Nolan, S., Tudur Smith, C., Pulman, J., & AG, M. (2013). Phenobarbitone versus phenytoin monotherapy for partial onset seizures and generalised onset tonic-clonic seizures (Review).** ***Cochrane Database Syst Rev*****.**

**399. Tudur Smith, C., Marson, A. G., & Williamson, P. R. (2003). Carbamazepine versus phenobarbitone monotherapy for epilepsy (review).** ***Cochrane Database Syst Rev*****(1).**

**400. de Silva, M., MacArdle, B., McGowan, M., Hughes, E., Stewart, J., Neville, B. G., et al. (1996). Randomised comparative monotherapy trial of phenobarbitone, phenytoin,**

**carbamazepine, or sodium valproate for newly diagnosed childhood epilepsy. *Lancet, 347*(9003), 709-713.**

**401. Heller, A. J., Chesterman, P., Elwes, R. D., Crawford, P., Chadwick, D., Johnson, A. L., et al. (1995). Phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed adult epilepsy: a randomised comparative monotherapy trial. *J Neurol Neurosurg Psychiatry, 58*(1), 44-50.**

**402. Feksi, A. T., Kaamugisha, J., Sander, J. W., Gatiti, S., & Shorvon, S. D. (1991). Comprehensive primary health care antiepileptic drug treatment programme in rural and semi-urban Kenya. ICBERG (International Community-based Epilepsy Research Group). *Lancet, 337*(8738), 406-409.**

**403. Thilothammal, N., Banu, K., & Ratnam, R. S. (1996). Comparison of phenobarbitone, phenytoin with sodium valproate: randomized, double-blind study. *Indian Pediatr, 33*(7), 549-555.**

**404. Zhang, L. L., Zeng, L. N., & Li, Y. P. (2011). Side effects of phenobarbital in epilepsy: a systematic review. *Epileptic Disord, 13*(4), 349-365, doi:10.1684/epd.2011.0444.**

**405. Smith, D. B., Mattson, R. H., Cramer, J. A., Collins, J. F., Novelly, R. A., & Craft, B. (1987). Results of a nationwide Veterans Administration Cooperative Study comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone. *Epilepsia, 28 Suppl 3*, S50-58.**

**406. Tedeschi, G., Casucci, G., Allocca, S., Riva, R., Di Costanzo, A., Tata, M. R., et al. (1989). Neuroocular side effects of carbamazepine and phenobarbital in epileptic patients as measured by saccadic eye movements analysis. *Epilepsia, 30*(1), 62-66.**

**407. Meador, K. J., Loring, D. W., Moore, E. E., Thompson, W. O., Nichols, M. E., Oberzan, R. E., et al. (1995). Comparative cognitive effects of phenobarbital, phenytoin, and valproate in healthy adults. *Neurology, 45*(8), 1494-1499.**

**408. Vining, E. P., Mellitis, E. D., Dorsen, M. M., Cataldo, M. F., Quaskey, S. A., Spielberg, S. P., et al. (1987). Psychologic and behavioral effects of antiepileptic drugs in children: a double-blind comparison between phenobarbital and valproic acid. *Pediatrics, 80*(2), 165-174.**

**409. Camfield, C. S., Chaplin, S., Doyle, A. B., Shapiro, S. H., Cummings, C., & Camfield, P. R. (1979). Side effects of phenobarbital in toddlers; behavioral and cognitive aspects. *J Pediatr, 95*(3), 361-365.**

**410. Placencia, M., Sander, J. W., Shorvon, S. D., Roman, M., Alarcon, F., Bimos, C., et al. (1993). Antiepileptic drug treatment in a community health care setting in northern Ecuador: a prospective 12-month assessment. *Epilepsy Res, 14*(3), 237-244.**

**411. Chen, Y. J., Kang, W. M., & So, W. C. (1996). Comparison of antiepileptic drugs on cognitive function in newly diagnosed epileptic children: a psychometric and neurophysiological study. *Epilepsia, 37*(1), 81-86.**

**412. Pal, D. K., Das, T., Chaudhury, G., Johnson, A. L., & Neville, B. G. (1998). Randomised controlled trial to assess acceptability of phenobarbital for childhood epilepsy in rural India. *Lancet, 351*(9095), 19-23, doi:10.1016/S0140-6736(97)06250-8.**

**413. Zola, I. R. (1966). Culture and Symptoms--An Analysis of Patient's Presenting Complaints. *American Sociological Review, 31*(5), 615-630.**

**414. Okazaki, S. (2000). Asian American and White American Differences on Affective Distress Symptoms: Do Symptom Reports Differ Across Reporting Methods? *Journal of Cross-Cultural Psychology, 31*(5), 603-625, doi:10.1177/0022022100031005004.**

**415. Juarez, G., Ferrell, B., & Borneman, T. (1998). Influence of culture on cancer pain management in Hispanic patients. *Cancer Pract, 6*(5), 262-269.**

**416. Perucca, E. (2007). Treatment of epilepsy in developing countries. *BMJ, 334*(7605), 1175-1176, doi:10.1136/bmj.39065.460208.80.**

**417. Mei, P., Montenegro, M. A., Guerreiro, M. M., & Guerreiro, C. (2006). Pharmacoviligance in epileptic patients using antiepileptic drugs. *Arq Neuropsiquiatr, 64*(2-A), 198-201.**

**418. Carpay, J. A., Aldenkamp, A. P., & van Donselaar, C. A. (2005). Complaints associated with the use of antiepileptic drugs: results from a community-based study. *Seizure, 14*(3), 198-206, doi:10.1016/j.seizure.2005.01.008.**

**419. Uijl, S. G., Uiterwaal, C. S., Aldenkamp, A. P., Carpay, J. A., Doelman, J. C., Keizer, K., et al. (2006). A cross-sectional study of subjective complaints in patients with epilepsy who seem to be well-controlled with anti-epileptic drugs. *Seizure, 15*(4), 242-248, doi:10.1016/j.seizure.2006.02.009.**

**420. Baker, G., Jacoby, A., Francis, P., & Chadwick, D. (1994). Initial development, reliability, and validity of a patient-based adverse drug event scale. *Epilepsia, 35*(suppl 7), 20.**

**421. Panelli, R. J., Kilpatrick, C., Moore, S. M., Matkovic, Z., D'Souza, W. J., & O'Brien, T. J. (2007). The Liverpool Adverse Events Profile: relation to AED use and mood. *Epilepsia, 48*(3), 456-463, doi:10.1111/j.1528-1167.2006.00956.x.**

**422. Carreno, M., Gil-Nagel, A., Sanchez, J. C., Elices, E., Serratosa, J. M., Salas-Puig, J., et al. (2008). Strategies to detect adverse effects of antiepileptic drugs in clinical practice. *Epilepsy Behav, 13*(1), 178-183, doi:10.1016/j.yebeh.2008.02.006.**

**423. Wang, W. Z., Wu, J. Z., Ma, G. Y., Dai, X. Y., Yang, B., Wang, T. P., et al. (2006). Efficacy assessment of phenobarbital in epilepsy: a large community-based intervention trial in rural China. *Lancet Neurol, 5*(1), 46-52, doi:10.1016/S1474-4422(05)70254-4.**

**424. Perucca, P., Jacoby, A., Marson, A. G., Baker, G. A., Lane, S., Benn, E. K., et al. (2011). Adverse antiepileptic drug effects in new-onset seizures: a case-control study. *Neurology, 76*(3), 273-279, doi:10.1212/WNL.0b013e318207b073.**

**425. Brodie, M. J., & Kwan, P. (2012). Current position of phenobarbital in epilepsy and its future. *Epilepsia, 53 Suppl 8*, 40-46, doi:10.1111/epi.12027.**

**426. Tang, F., Zhu, G., Jiao, Z., Ma, C., & Wang, B. (2013). Self-reported adherence in patients with epilepsy who missed their medications and reasons for nonadherence in China. *Epilepsy Behav, 27*(1), 85-89, doi:10.1016/j.yebeh.2012.12.022.**

**427. Simmons, R. D., Ciancio, B. C., Kall, M. M., Rice, B. D., & Delpech, V. C. (2013). Ten-year mortality trends among persons diagnosed with HIV infection in England and Wales in the era of antiretroviral therapy: AIDS remains a silent killer. *HIV Med, 14*(10), 596-604, doi:10.1111/hiv.12045.**

**428. Hankins, C. (2013). Overview of the current state of the epidemic. *Curr HIV/AIDS Rep, 10*(2), 113-123, doi:10.1007/s11904-013-0156-x.**

**429. Bekolo, C. E., Webster, J., Batenganya, M., Sume, G. E., & Kollo, B. (2013). Trends in mortality and loss to follow-up in HIV care at the Nkongsamba Regional hospital, Cameroon. *BMC Res Notes, 6*(1), 512, doi:10.1186/1756-0500-6-512.**

**430. Broder, S. (2010). The development of antiretroviral therapy and its impact on the HIV-1/AIDS pandemic. *Antiviral Res, 85*(1), 1-18, doi:10.1016/j.antiviral.2009.10.002.**

**431. Gonzalo, T., Garcia Goni, M., & Munoz-Fernandez, M. A. (2009). Socio-economic impact of antiretroviral treatment in HIV patients. An economic review of cost savings after introduction of HAART. *AIDS Rev, 11*(2), 79-90.**

**432. Montaner, J. S., Lima, V. D., Harrigan, P. R., Lourenco, L., Yip, B., Nosyk, B., et al. (2014). Expansion of HAART Coverage Is Associated with Sustained Decreases in HIV/AIDS Morbidity, Mortality and HIV Transmission: The "HIV Treatment as Prevention" Experience in a Canadian Setting. *PLoS One, 9*(2), e87872, doi:10.1371/journal.pone.0087872.**

**433. Ghate, M., Deshpande, S., Tripathy, S., Godbole, S., Nene, M., Thakar, M., et al. (2011). Mortality in HIV infected individuals in Pune, India. *Indian J Med Res, 133*, 414-420.**

**434. Breaux, K., Gadde, S., Graviss, E. A., & Rodriguez-Barradas, M. C. (2010). One year survival of HIV-infected veterans with CD4 < 100 cells/mm3: data from a veteran cohort. *AIDS Care, 22*(7), 886-894, doi:10.1080/09540120903499162.**

**435. Zhang, F., Dou, Z., Yu, L., Xu, J., Jiao, J. H., Wang, N., et al. (2008). The effect of highly active antiretroviral therapy on mortality among HIV-infected former plasma donors in China. *Clin Infect Dis, 47*(6), 825-833, doi:10.1086/590945.**

**436. Pezzotti, P., Napoli, P. A., Acciai, S., Boros, S., Urciuoli, R., Lazzeri, V., et al. (1999). Increasing survival time after AIDS in Italy: the role of new combination antiretroviral therapies. Tuscany AIDS Study Group. *AIDS, 13*(2), 249-255.**

**437. Ahuja, T. S., Borucki, M., & Grady, J. (2000). Highly active antiretroviral therapy improves survival of HIV-infected hemodialysis patients. *Am J Kidney Dis, 36*(3), 574-580, doi:10.1053/ajkd.2000.16196.**

**438. Guerreiro, M. F., Kerr-Pontes, L. R., Mota, R. S., Franca, M. C., Jr., Tavora, F. F., & Caminha, I. (2002). Survival of adult AIDS patients in a reference hospital of a metropolitan area in Brazil. *Rev Saude Publica, 36*(3), 278-284.**

**439. Hagmann, M. (2003). Study confirms effectiveness of antiretroviral drugs for HIV patients. *Bull World Health Organ, 81*(12), 918-919.**

**440. Resino, S., Bellon, J. M., Resino, R., Navarro, M. L., Tomas Ramos, J., de Jose, M. I., et al. (2004). Extensive implementation of highly active antiretroviral therapy shows great effect on survival and surrogate markers in vertically HIV-infected children. *Clin Infect Dis, 38*(11), 1605-1612, doi:10.1086/420738.**

**441. Mayor, A. M., Gomez, M. A., Rios-Oliveras, E., & Hunter-Mellado, R. F. (2005). Mortality trends of HIV-infected patients after the introduction of highly active antiretroviral therapy: analysis of a cohort of 3,322 HIV-infected persons. *Ethn Dis, 15*(4 Suppl 5), S5-57-62.**

**442. Couzigou, C., Semaille, C., Le Strat, Y., Pinget, R., Pillonel, J., Lot, F., et al. (2007). Differential improvement in survival among patients with AIDS after the introduction of HAART. *AIDS Care, 19*(4), 523-531, doi:10.1080/09540120701235628.**

**443. Lima, V. D., Hogg, R. S., Harrigan, P. R., Moore, D., Yip, B., Wood, E., et al. (2007). Continued improvement in survival among HIV-infected individuals with newer forms of highly active antiretroviral therapy. *AIDS, 21*(6), 685-692, doi:10.1097/QAD.0b013e32802ef30c.**

**444. Quinn, T. C. (2008). HIV epidemiology and the effects of antiviral therapy on long-term consequences. *AIDS, 22 Suppl 3*, S7-12, doi:10.1097/01.aids.0000327510.68503.e8.**

**445. Townsend, C. L., Byrne, L., Cortina-Borja, M., Thorne, C., de Ruiter, A., Lyall, H., et al. (2014). Earlier initiation of ART and further decline in mother-to-child HIV transmission rates, 2000-2011. *AIDS*, doi:10.1097/QAD.0000000000000212.**

**446. Abaasa, A. M., Todd, J., Ekoru, K., Kalyango, J. N., Levin, J., Odeke, E., et al. (2008). Good adherence to HAART and improved survival in a community HIV/AIDS treatment and care programme: the experience of The AIDS Support Organization (TASO), Kampala, Uganda. *BMC Health Serv Res, 8*, 241, doi:10.1186/1472-6963-8-241.**

**447. Lucas, G. M., Chaisson, R. E., & Moore, R. D. (1999). Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. *Ann Intern Med, 131*(2), 81-87.**

**448. Garcia de Olalla, P., Knobel, H., Carmona, A., Guelar, A., Lopez-Colomes, J. L., & Cayla, J. A. (2002). Impact of adherence and highly active antiretroviral therapy on survival in HIV-infected patients. *J Acquir Immune Defic Syndr, 30*(1), 105-110.**

**449. Nachega, J. B., Hislop, M., Dowdy, D. W., Lo, M., Omer, S. B., Regensberg, L., et al. (2006). Adherence to highly active antiretroviral therapy assessed by pharmacy claims predicts survival in HIV-infected South African adults. *J Acquir Immune Defic Syndr, 43*(1), 78-84, doi:10.1097/01.qai.0000225015.43266.46.**

**450. Park, W. B., Choe, P. G., Kim, S. H., Jo, J. H., Bang, J. H., Kim, H. B., et al. (2007). One-year adherence to clinic visits after highly active antiretroviral therapy: a predictor of clinical progress in HIV patients. *J Intern Med, 261*(3), 268-275, doi:10.1111/j.1365-2796.2006.01762.x.**

**451. Mocroft, A., Ledergerber, B., Zilmer, K., Kirk, O., Hirschel, B., Viard, J. P., et al. (2007). Short-term clinical disease progression in HIV-1-positive patients taking combination antiretroviral therapy: the EuroSIDA risk-score. *AIDS, 21*(14), 1867-1875, doi:10.1097/QAD.0b013e328270b877.**

**452. Howard, A. A., Arnsten, J. H., Lo, Y., Vlahov, D., Rich, J. D., Schuman, P., et al. (2002). A prospective study of adherence and viral load in a large multi-center cohort of HIV-infected women. *AIDS, 16*(16), 2175-2182.**

**453. Carrieri, M. P., Leport, C., Protopopescu, C., Cassuto, J. P., Bouvet, E., Peyramond, D., et al. (2006). Factors associated with nonadherence to highly active antiretroviral therapy: a 5-year follow-up analysis with correction for the bias induced by missing data in the treatment maintenance phase. *J Acquir Immune Defic Syndr, 41*(4), 477-485, doi:10.1097/01.qai.0000186364.27587.0e 00126334-200604010-00012 [pii].**

**454. Polisset, J., Ametonou, F., Arrive, E., Aho, A., & Perez, F. (2009). Correlates of Adherence to Antiretroviral Therapy in HIV-Infected Children in Lome, Togo, West Africa. *AIDS Behav, 13*(1), 23-32, doi:10.1007/s10461-008-9437-6.**

**455. Uzochukwu, B. S., Onwujekwe, O. E., Onoka, A. C., Okoli, C., Uguru, N. P., & Chukwuogo, O. I. (2009). Determinants of non-adherence to subsidized anti-retroviral treatment in southeast Nigeria. *Health Policy Plan, 24*(3), 189-196, doi:czp006 [pii]10.1093/heapol/czp006.**

**456. Carmody, E. R., Diaz, T., Starling, P., dos Santos, A. P., & Sacks, H. S. (2003). An evaluation of antiretroviral HIV/AIDS treatment in a Rio de Janeiro public clinic. *Trop Med Int Health, 8*(5), 378-385.**

**457. Orrell, C., Bangsberg, D. R., Badri, M., & Wood, R. (2003). Adherence is not a barrier to successful antiretroviral therapy in South Africa. *AIDS, 17*(9), 1369-1375, doi:10.1097/01.aids.0000060398.18106.f6.**

**458. Glass, T. R., De Geest, S., Weber, R., Vernazza, P. L., Rickenbach, M., Furrer, H., et al. (2006). Correlates of self-reported nonadherence to antiretroviral therapy in HIV-infected patients: the Swiss HIV Cohort Study. *J Acquir Immune Defic Syndr, 41*(3), 385-392, doi:10.1097/01.qai.0000186371.95301.5200126334-200603000-00018 [pii].**

**459. Bhat, V. G., Ramburuth, M., Singh, M., Titi, O., Antony, A. P., Chiya, L., et al. (2010). Factors associated with poor adherence to anti-retroviral therapy in patients attending a rural health centre in South Africa. *Eur J Clin Microbiol Infect Dis, 29*(8), 947-953, doi:10.1007/s10096-010-0949-4.**

**460. Gordillo, V., del Amo, J., Soriano, V., & Gonzalez-Lahoz, J. (1999). Sociodemographic and psychological variables influencing adherence to antiretroviral therapy. *AIDS, 13*(13), 1763-1769.**

**461. Byakika-Tusiime, J., Oyugi, J. H., Tumwikirize, W. A., Katabira, E. T., Mugyenyi, P. N., & Bangsberg, D. R. (2005). Adherence to HIV antiretroviral therapy in HIV+ Ugandan patients purchasing therapy. *Int J STD AIDS, 16*(1), 38-41.**

**462. Peltzer, K., Friend-du Preez, N., Ramlagan, S., & Anderson, J. (2010). Antiretroviral treatment adherence among HIV patients in KwaZulu-Natal, South Africa. *BMC Public Health, 10*, 111, doi:1471-2458-10-111 [pii]10.1186/1471-2458-10-111.**

**463. Bonolo Pde, F., Machado, C. J., Cesar, C. C., Ceccato, M., & Guimaraes, M. D. (2008). Vulnerability and non-adherence to antiretroviral therapy among HIV patients, Minas Gerais State, Brazil. *Cad Saude Publica, 24*(11), 2603-2613.**

**464. Olowookere, S. A., Fatiregun, A. A., Akinyemi, J. O., Bamgboye, A. E., & Osagbemi, G. K. (2008). Prevalence and determinants of nonadherence to highly active antiretroviral therapy among people living with HIV/AIDS in Ibadan, Nigeria. *J Infect Dev Ctries, 2*(5), 369-372.**

**465. Laniece, I., Ciss, M., Desclaux, A., Diop, K., Mbodj, F., Ndiaye, B., et al. (2003). Adherence to HAART and its principal determinants in a cohort of Senegalese adults. *AIDS, 17 Suppl 3,* S103-108.**

**466. Biadgilign, S., Deribew, A., Amberbir, A., & Deribe, K. (2008). Adherence to highly active antiretroviral therapy and its correlates among HIV infected pediatric patients in Ethiopia. *BMC Pediatr, 8,* 53, doi:1471-2431-8-53 [pii]10.1186/1471-2431-8-53.**

**467. Crane, J. T., Kawuma, A., Oyugi, J. H., Byakika, J. T., Moss, A., Bourgois, P., et al. (2006). The price of adherence: qualitative findings from HIV positive individuals purchasing fixed-dose combination generic HIV antiretroviral therapy in Kampala, Uganda. *AIDS Behav, 10*(4), 437-442, doi:10.1007/s10461-006-9080-z.**

**468. Iliyasu, Z., Kabir, M., Abubakar, I. S., Babashani, M., & Zubair, Z. A. (2005). Compliance to antiretroviral therapy among AIDS patients in Aminu Kano Teaching Hospital, Kano, Nigeria. *Niger J Med, 14*(3), 290-294.**

**469. Naik, E., Casanas, B., Pazare, A., Wabale, G., Sinnott, J., & Salihu, H. (2009). Cost of treatment: The single biggest obstacle to HIV/AIDS treatment adherence in lower-middle class patients in Mumbai, India. *Indian J Sex Transm Dis, 30*(1), 23-27, doi:10.4103/0253-7184.55476.**

**470. Gifford, A. L., Bormann, J. E., Shively, M. J., Wright, B. C., Richman, D. D., & Bozzette, S. A. (2000). Predictors of self-reported adherence and plasma HIV concentrations in patients on multidrug antiretroviral regimens. *J Acquir Immune Defic Syndr, 23*(5), 386-395.**

**471. Altice, F. L., Mostashari, F., & Friedland, G. H. (2001). Trust and the acceptance of and adherence to antiretroviral therapy. *J Acquir Immune Defic Syndr, 28*(1), 47-58.**

**472. Nachega, J. B., Stein, D. M., Lehman, D. A., Hlatshwayo, D., Mothopeng, R., Chaisson, R. E., et al. (2004). Adherence to antiretroviral therapy in HIV-infected adults in Soweto, South Africa. *AIDS Res Hum Retroviruses, 20*(10), 1053-1056, doi:10.1089/aid.2004.20.1053.**

**473. Bangsberg, D. R., Ragland, K., Monk, A., & Deeks, S. G. (2010). A single tablet regimen is associated with higher adherence and viral suppression than multiple tablet regimens in HIV+ homeless and marginally housed people. *AIDS, 24*(18), 2835-2840, doi:10.1097/QAD.0b013e328340a209.**

**474. Golin, C. E., Liu, H., Hays, R. D., Miller, L. G., Beck, C. K., Ickovics, J., et al. (2002). A prospective study of predictors of adherence to combination antiretroviral medication. *J Gen Intern Med, 17*(10), 756-765.**

**475. Unge, C., Johansson, A., Zachariah, R., Some, D., Van Engelgem, I., & Ekstrom, A. M. (2008). Reasons for unsatisfactory acceptance of antiretroviral treatment in the urban Kibera slum, Kenya. *AIDS Care, 20*(2), 146-149, doi:790554794 [pii]10.1080/09540120701513677.**

**476. Byakika-Tusiime, J., Crane, J., Oyugi, J. H., Ragland, K., Kawuma, A., Musoke, P., et al. (2009). Longitudinal antiretroviral adherence in HIV+ Ugandan parents and their children initiating HAART in the MTCT-Plus family treatment model: role of depression in declining adherence over time. *AIDS Behav, 13 Suppl 1*, 82-91, doi:10.1007/s10461-009-9546-x.**

**477. Roca, B., Gomez, C. J., & Arnedo, A. (2000). Adherence, side effects and efficacy of stavudine plus lamivudine plus nelfinavir in treatment-experienced HIV-infected patients. *J Infect, 41*(1), 50-54, doi:10.1053/jinf.2000.0678.**

**478. Ammassari, A., Murri, R., Pezzotti, P., Trotta, M. P., Ravasio, L., De Longis, P., et al. (2001). Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection. *J Acquir Immune Defic Syndr, 28*(5), 445-449.**

**479. Giday, A., & Shiferaw, W. (2010). Factors affecting adherence of antiretroviral treatment among AIDS patients in an Ethiopian tertiary university teaching hospital. *Ethiop Med J, 48*(3), 187-194.**

**480. Lenzi, L., Wiens, A., & Pontarolo, R. (2013). Evaluation of adverse events associated with antiretroviral therapy and the relationship to treatment adherence. *Int J Clin Pharmacol Ther, 51*(2), 141-146, doi:10.5414/CP201818.**

**481. Wasti, S. P., Simkhada, P., Randall, J., Freeman, J. V., & van Teijlingen, E. (2012). Factors influencing adherence to antiretroviral treatment in Nepal: a mixed-methods study. *PLoS One, 7*(5), e35547, doi:10.1371/journal.pone.0035547.**

**482. WHO (2010). Antiretroviral Therapy for HIV Infection in Infants and Children: Towards Universal Access: Recommendations for a Public Health Approach: 2010 Revision. . Geneva: World Health Organization.**

**483. van Oosterhout, J. J., Bodasing, N., Kumwenda, J. J., Nyirenda, C., Mallewa, J., Cleary, P. R., et al. (2005). Evaluation of antiretroviral therapy results in a resource-poor setting in Blantyre, Malawi. *Trop Med Int Health, 10*(5), 464-470, doi:10.1111/j.1365-3156.2005.01409.x.**

**484. Cauldbeck, M. B., O'Connor, C., O'Connor, M. B., Saunders, J. A., Rao, B., Mallesh, V. G., et al. (2009). Adherence to anti-retroviral therapy among HIV patients in Bangalore, India. *AIDS Res Ther, 6*, 7, doi:10.1186/1742-6405-6-7.**

**485. Nagpal, M., Tayal, V., Kumar, S., & Gupta, U. (2010). Adverse drug reactions to antiretroviral therapy in AIDS patients at a tertiary care hospital in India: A prospective observational study. *Indian J Med Sci, 64*(6), 245-252, doi:10.4103/0019-5359.99597.**

**486. Hasan, S. S., Keong, S. C., Choong, C. L., Ahmed, S. I., Ching, T. W., Anwar, M., et al. (2011). Patient-reported adverse drug reactions and drug-drug interactions: a cross-sectional study on Malaysian HIV/AIDS patients. *Med Princ Pract, 20*(3), 265-270, doi:10.1159/000321274.**

**487. Wu, A. W., Rubin, H. R., Mathews, W. C., Ware, J. E., Jr., Brysk, L. T., Hardy, W. D., et al. (1991). A health status questionnaire using 30 items from the Medical Outcomes Study. Preliminary validation in persons with early HIV infection. *Med Care, 29*(8), 786-798.**

**488. Justice, A. C., Holmes, W., Gifford, A. L., Rabeneck, L., Zackin, R., Sinclair, G., et al. (2001). Development and validation of a self-completed HIV symptom index. *J Clin Epidemiol, 54 Suppl 1*, S77-90.**

**489. Johnson, M. O., & Neilands, T. B. (2007). Neuroticism, Side Effects, and Health Perceptions Among HIV-Infected Individuals on Antiretroviral Medications. *J Clin Psychol Med Settings, 14*(1), 69-77, doi:10.1007/s10880-007-9056-9.**

**490. Cleary, P. D., Fowler, F. J., Jr., Weissman, J., Massagli, M. P., Wilson, I., Seage, G. R., 3rd, et al. (1993). Health-related quality of life in persons with acquired immune deficiency syndrome. *Med Care, 31*(7), 569-580.**

**491. Whalen, C. C., Antani, M., Carey, J., & Landefeld, C. S. (1994). An index of symptoms for infection with human immunodeficiency virus: reliability and validity. *J Clin Epidemiol, 47*(5), 537-546.**

**492. Ware, J. E., Jr., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care, 30*(6), 473-483.**

**493. Johnson, M. O., Stallworth, T., & Neilands, T. B. (2003). The drugs or the disease? Causal attributions of symptoms held by HIV-positive adults on HAART. *AIDS Behav, 7*(2), 109-117.**

**494. Holzemer, W. L., Hudson, A., Kirksey, K. M., Hamilton, M. J., & Bakken, S. (2001). The revised Sign and Symptom Check-List for HIV (SSC-HIVrev). *J Assoc Nurses AIDS Care, 12*(5), 60-70.**

**495. Scott-Lennox, J. A., Wu, A. W., Boyer, J. G., & Ware, J. E., Jr. (1999). Reliability and validity of French, German, Italian, Dutch, and UK English translations of the Medical Outcomes Study HIV Health Survey. *Med Care, 37*(9), 908-925.**

**496. Kohli, R. M., Sane, S., Kumar, K., Paranjape, R. S., & Mehendale, S. M. (2005). Modification of medical outcome study (MOS) instrument for quality of life assessment & its validation in HIV infected individuals in India. *Indian J Med Res, 122*(4), 297-304.**

**497. Kohli, R. M., Sane, S., Kumar, K., Paranjape, R. S., & Mehendale, S. M. (2005). Assessment of quality of life among HIV-infected persons in Pune, India. *Qual Life Res, 14*(6), 1641-1647.**

**498. Murri, R., Fantoni, M., Del Borgo, C., Visona, R., Barracco, A., Zambelli, A., et al. (2003). Determinants of health-related quality of life in HIV-infected patients. *AIDS Care, 15*(4), 581-590, doi:10.1080/0954012031000134818.**

**499. Badia, X., Podzamczer, D., Casado, A., Lopez-Lavid, C., & Garcia, M. (2000). Evaluating changes in health status in HIV-infected patients: Medical Outcomes Study-HIV and Multidimensional Quality of Life-HIV quality of life questionnaires. Spanish MOS-HIV and MQOL-HIV Validation Group. *AIDS, 14*(10), 1439-1447.**

**500. Ichikawa, M., & Natpratan, C. (2004). Quality of life among people living with HIV/AIDS in northern Thailand: MOS-HIV Health Survey. *Qual Life Res, 13*(3), 601-610.**

**501. Wachtel, T., Piette, J., Mor, V., Stein, M., Fleishman, J., & Carpenter, C. (1992). Quality of life in persons with human immunodeficiency virus infection:**

**measurement by the Medical Outcomes Study instrument. *Ann Intern Med, 116*(2), 129-137.**

**502. Marcellin, F., Boyer, S., Protopopescu, C., Dia, A., Ongolo-Zogo, P., Koulla-Shiro, S., et al. (2008). Determinants of unplanned antiretroviral treatment interruptions among people living with HIV in Yaounde, Cameroon (EVAL survey, ANRS 12-116). *Trop Med Int Health, 13*(12), 1470-1478, doi:10.1111/j.1365-3156.2008.02170.x.**

**503. Reynolds, N. R., Testa, M. A., Marc, L. G., Chesney, M. A., Neidig, J. L., Smith, S. R., et al. (2004). Factors influencing medication adherence beliefs and self-efficacy in persons naive to antiretroviral therapy: a multicenter, cross-sectional study. *AIDS Behav, 8*(2), 141-150, doi:10.1023/B:AIBE.0000030245.52406.bb.**

**504. Protopopescu, C., Marcellin, F., Spire, B., Preau, M., Verdon, R., Peyramond, D., et al. (2007). Health-related quality of life in HIV-1-infected patients on HAART: a five-years longitudinal analysis accounting for dropout in the APROCO-COPILOTE cohort (ANRS CO-8). *Qual Life Res, 16*(4), 577-591, doi:10.1007/s11136-006-9151-7.**

**505. Preau, M., Marcellin, F., Carrieri, M. P., Lert, F., Obadia, Y., Spire, B., et al. (2007). Health-related quality of life in French people living with HIV in 2003: results from the national ANRS-EN12-VESPA Study. *AIDS, 21 Suppl 1*, S19-27, doi:10.1097/01.aids.0000255081.24105.d7.**

**506. O'Keefe, E. A., & Wood, R. (1996). The impact of human immunodeficiency virus (HIV) infection on quality of life in a multiracial South African population. *Qual Life Res, 5*(2), 275-280.**

**507. Bastardo, Y. M., & Kimberlin, C. L. (2000). Relationship between quality of life, social support and disease-related factors in HIV-infected persons in Venezuela. *AIDS Care, 12*(5), 673-684, doi:10.1080/095401200750003842.**

**508. Sowell, R., Seals, B., Moneyham, L., Demi, A., Cohen, L., & Brake, S. (1997). Quality of life in HIV-infected women in the south-eastern United States. *AIDS Care, 9*(5), 501-512.**

**509. Rivero-Mendez, M., Portillo, C., Solis-Baez, S. S., Wantland, D., & Holzemer, W. L. (2009). Symptoms and quality of life of people living with HIV infection in Puerto Rico. *P R Health Sci J, 28*(1), 54-59.**

**510. Makoae, L. N., Seboni, N. M., Molosiwa, K., Moleko, M., Human, S., Sukati, N. A., et al. (2005). The symptom experience of people living with HIV/AIDS in Southern Africa. *J Assoc Nurses AIDS Care, 16*(3), 22-32.**

**511. Peltzer, K., & Phaswana-Mafuya, N. (2008). The symptom experience of people living with HIV and AIDS in the Eastern Cape, South Africa. *BMC Health Serv Res, 8*, 271, doi:10.1186/1472-6963-8-271.**

**512. Holzemer, W. L., Henry, S. B., Nokes, K. M., Corless, I. B., Brown, M. A., Powell-Cope, G. M., et al. (1999). Validation of the Sign and Symptom Check-List for Persons with HIV Disease (SSC-HIV). *J Adv Nurs, 30*(5), 1041-1049.**

**513. Hudson, A., Kirksey, K., & Holzemer, W. (2004). The influence of symptoms on quality of life among HIV-infected women. *West J Nurs Res, 26*(1), 9-23; discussion 24-30, doi:10.1177/0193945903259221.**

**514. Grimes, R. M., Lal, L., & Lewis, S. T. (2002). Frequency of medical history items, drug interactions, and lifestyle characteristics that may interfere with antiretroviral medications. *HIV Clin Trials, 3*(2), 161-167.**

**515. Nachega, J. B., Hsu, A. J., Uthman, O. A., Spinewine, A., & Pham, P. A. (2012). Antiretroviral therapy adherence and drug-drug interactions in the aging HIV population. *AIDS, 26 Suppl 1*, S39-53, doi:10.1097/QAD.0b013e32835584ea.**

**516. Chauvin, B., Drouot, S., Barrail-Tran, A., & Taburet, A. M. (2013). Drug-drug interactions between HMG-CoA reductase inhibitors (statins) and antiviral protease inhibitors. *Clin Pharmacokinet, 52*(10), 815-831, doi:10.1007/s40262-013-0075-4.**

**517. Fehintola, F. A., Akinyinka, O. O., Adewole, I. F., Maponga, C. C., Ma, Q., & Morse, G. D. (2011). Drug interactions in the treatment and chemoprophylaxis of malaria in HIV infected individuals in sub Saharan Africa. *Curr Drug Metab, 12*(1), 51-56.**

**518. Venkatesh, K. K., Swaminathan, S., Andrews, J. R., & Mayer, K. H. (2011). Tuberculosis and HIV co-infection: screening and treatment strategies. *Drugs, 71*(9), 1133-1152, doi:10.2165/11591360-000000000-00000.**

**519. Vadlapatla, R. K., Patel, M., Paturi, D. K., Pal, D., & Mitra, A. K. (2014). Clinically relevant drug-drug interactions between antiretrovirals and antifungals. *Expert Opin Drug Metab Toxicol*, doi:10.1517/17425255.2014.883379.**

**520. Curran, A., Falco, V., Pahissa, A., & Ribera, E. (2012). Management of tuberculosis in HIV-infected patients. *AIDS Rev, 14*(4), 231-246.**

**521. Nanavati, K. A., Fisher, S. D., Miller, T. L., & Lipshultz, S. E. (2004). HIV-related cardiovascular disease and drug interactions. *Am J Cardiovasc Drugs, 4*(5), 315-324.**

**522. Pau, A. K. (2008). Clinical management of drug interaction with antiretroviral agents. *Curr Opin HIV AIDS, 3*(3), 319-324, doi:10.1097/COH.0b013e3282f82c06.**

**523. Shah, S. S., McGowan, J. P., Smith, C., Blum, S., & Klein, R. S. (2002). Comorbid conditions, treatment, and health maintenance in older persons with human immunodeficiency virus infection in New York City. *Clin Infect Dis, 35*(10), 1238-1243, doi:10.1086/343048.**

**524. Marzolini, C., Back, D., Weber, R., Furrer, H., Cavassini, M., Calmy, A., et al. (2011). Ageing with HIV: medication use and risk for potential drug-drug interactions. *J Antimicrob Chemother, 66*(9), 2107-2111, doi:10.1093/jac/dkr248.**

**525. Kaufman, K. R. (2011). Antiepileptic drugs in the treatment of psychiatric disorders. *Epilepsy Behav, 21*(1), 1-11, doi:10.1016/j.yebeh.2011.03.011.**

**526. Birbeck, G., Chomba, E., Ddumba, E., Kauye, F., & Mielke, J. (2007). Lack of appropriate treatment for people with comorbid HIV/AIDS and epilepsy in sub-Saharan Africa. *Epilepsia, 48*(7), 1424-1425, doi:10.1111/j.1528-1167.2007.01060_10.x.**

**527. Andrew, T., Milinis, K., Baker, G., & Wieshmann, U. (2012). Self reported adverse effects of mono and polytherapy for epilepsy. *Seizure, 21*(8), 610-613, doi:10.1016/j.seizure.2012.06.013.**

**528. Salinsky, M. C., & Storzbach, D. (2005). The Portland Neurotoxicity Scale: validation of a brief self-report measure of antiepileptic-drug-related neurotoxicity. *Assessment, 12*(1), 107-117, doi:10.1177/1073191104272857.**

**529. Gillham, R., Baker, G., Thompson, P., Birbeck, K., McGuire, A., Tomlinson, L., et al. (1996). Standardisation of a self-report questionnaire for use in evaluating cognitive, affective and behavioural side-effects of anti-epileptic drug treatments. *Epilepsy Res, 24*(1), 47-55.**

**530. Aldenkamp, A. P., Baker, G., Pieters, M. S., Schoemaker, H. C., Cohen, A. F., & Schwabe, S. (1995). The Neurotoxicity Scale: the validity of a patient-based scale, assessing neurotoxicity. *Epilepsy Res, 20*(3), 229-239.**

**531. Cramer, J. A., Smith, D. B., Mattson, R. H., Delgado Escueta, A. V., & Collins, J. F. (1983). A method of quantification for the evaluation of antiepileptic drug therapy. *Neurology, 33*(3 Suppl 1), 26-37.**

**532. Martins, H. H., Alonso, N. B., Vidal-Dourado, M., Carbonel, T. D., de Araujo Filho, G. M., Caboclo, L. O., et al. (2011). Are adverse effects of antiepileptic drugs different in symptomatic partial and idiopathic generalized epilepsies? The Portuguese-Brazilian validation of the Liverpool Adverse Events Profile. *Epilepsy Behav, 22*(3), 511-517, doi:10.1016/j.yebeh.2011.08.005.**

**533. Chen, H. F., Tsai, Y. F., Shih, M. S., & Chen, J. C. (2011). Validation of the Chinese version of the Liverpool Adverse Events Profile in patients with epilepsy. *Epilepsy Res, 94*(1-2), 45-52, doi:10.1016/j.eplepsyres.2011.01.008.**

**534. Saetre, E., Perucca, E., Isojarvi, J., Gjerstad, L., & Group, L. A. M. S. (2007). An international multicenter randomized double-blind controlled trial of lamotrigine and sustained-release carbamazepine in the treatment of newly diagnosed epilepsy in the elderly. *Epilepsia, 48*(7), 1292-1302, doi:10.1111/j.1528-1167.2007.01128.x.**

**535. Canevini, M. P., De Sarro, G., Galimberti, C. A., Gatti, G., Licchetta, L., Malerba, A., et al. (2010). Relationship between adverse effects of antiepileptic drugs, number of coprescribed drugs, and drug load in a large cohort of consecutive patients with drug-refractory epilepsy. *Epilepsia, 51*(5), 797-804, doi:10.1111/j.1528-1167.2010.02520.x.**

**536. Carreno, M., Donaire, A., Falip, M., Maestro, I., Fernandez, S., Nagel, A. G., et al. (2009). Validation of the Spanish version of the Liverpool Adverse Events Profile in patients with epilepsy. *Epilepsy Behav, 15*(2), 154-159, doi:10.1016/j.yebeh.2008.11.016.**

**537. Romanelli, F., & Ryan, M. (2002). Seizures in HIV-seropositive individuals: epidemiology and treatment. *CNS Drugs, 16*(2), 91-98, doi:160202 [pii].**

**538. Lu, C., Berg, C., Prakash, S. R., Lee, F. W., & Balani, S. K. (2008). Prediction of pharmacokinetic drug-drug interactions using human hepatocyte suspension in plasma and cytochrome P450 phenotypic data. III. In vitro-in vivo correlation with fluconazole. *Drug Metab Dispos, 36*(7), 1261-1266, doi:10.1124/dmd.107.019000.**

**539. Perlman, D. C., Segal, Y., Rosenkranz, S., Rainey, P. M., Remmel, R. P., Salomon, N., et al. (2005). The clinical pharmacokinetics of rifampin and ethambutol in HIV-infected persons with tuberculosis. *Clin Infect Dis, 41*(11), 1638-1647, doi:10.1086/498024.**

**540. Zambia (2007). National Guidelines: Managment of HIV Infected People. In M. o. Health (Ed.). Lusaka.**

**541. Johnson, M. O., Charlebois, E., Morin, S. F., Catz, S. L., Goldstein, R. B., Remien, R. H., et al. (2005). Perceived adverse effects of antiretroviral therapy. *J Pain Symptom Manage, 29*(2), 193-205.**

**542. Kremer, H., Sonnenberg-Schwan, U., Arendt, G., Brockmeyer, N. H., Potthoff, A., Ulmer, A., et al. (2009). HIV or HIV-therapy? Causal attributions of symptoms and their impact on treatment decisions among women and men with HIV. *Eur J Med Res, 14*(4), 139-146.**

**543. Cambiano, V., Lampe, F. C., Rodger, A. J., Smith, C. J., Geretti, A. M., Lodwick, R. K., et al. (2010). Long-term trends in adherence to antiretroviral therapy from start of HAART. *AIDS, 24*(8), 1153-1162, doi:10.1097/QAD.0b013e32833847af.**

**544. WHO (2010). Global status report on noncommunicable diseases. Geneva: World Health Organization.**

**545. Narayan, K. M., Ali, M. K., & Koplan, J. P. (2010). Global noncommunicable diseases--where worlds meet. *N Engl J Med, 363*(13), 1196-1198, doi:10.1056/NEJMp1002024.**

**546. Bygbjerg, I. C. (2012). Double burden of noncommunicable and infectious diseases in developing countries. *Science, 337*(6101), 1499-1501, doi:10.1126/science.1223466.**

**547. Abegunde, D. O., Mathers, C. D., Adam, T., Ortegon, M., & Strong, K. (2007). The burden and costs of chronic diseases in low-income and middle-income countries. *Lancet, 370*(9603), 1929-1938, doi:10.1016/S0140-6736(07)61696-1.**

**548. Naghavi, M., & Forouzanfar, M. (2013). Burden of non-communicable diseases in sub-Saharan Africa in 1990 and 2010: Global Burden of Diseases, Injuries, and Risk Factors Study 2010. *Lancet, 381*(S2), 17-19.**

**549. Ataguba, J. E. (2013). Inequalities in multimorbidity in South Africa. *Int J Equity Health, 12*(1), 64, doi:10.1186/1475-9276-12-64.**

**550. Nimako, B. A., Baiden, F., Sackey, S. O., & Binka, F. (2013). Multimorbidity of chronic diseases among adult patients presenting to an inner-city clinic in Ghana. *Global Health, 9,* 61, doi:10.1186/1744-8603-9-61.**

**551. Khanam, M. A., Streatfield, P. K., Kabir, Z. N., Qiu, C., Cornelius, C., & Wahlin, A. (2011). Prevalence and patterns of multimorbidity among elderly people in rural Bangladesh: a cross-sectional study. *J Health Popul Nutr, 29*(4), 406-414.**

**552. Agborsangaya, C. B., Lau, D., Lahtinen, M., Cooke, T., & Johnson, J. A. (2013). Health-related quality of life and healthcare utilization in multimorbidity: results of a cross-sectional survey. *Qual Life Res, 22*(4), 791-799, doi:10.1007/s11136-012-0214-7.**

**553. Barnett, K., Mercer, S. W., Norbury, M., Watt, G., Wyke, S., & Guthrie, B. (2012). Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet, 380*(9836), 37-43, doi:10.1016/S0140-6736(12)60240-2.**

**554. Gunn, J. M., Ayton, D. R., Densley, K., Pallant, J. F., Chondros, P., Herrman, H. E., et al. (2012). The association between chronic illness, multimorbidity and depressive symptoms in an Australian primary care cohort. *Soc Psychiatry Psychiatr Epidemiol, 47*(2), 175-184, doi:10.1007/s00127-010-0330-z.**

**555. Wolff, J. L., Starfield, B., & Anderson, G. (2002). Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med, 162*(20), 2269-2276.**

**556. Naessens, J. M., Stroebel, R. J., Finnie, D. M., Shah, N. D., Wagie, A. E., Litchy, W. J., et al. (2011). Effect of multiple chronic conditions among working-age adults. *Am J Manag Care, 17*(2), 118-122.**

**557. Brown, L., Macintyre, K., & Trujillo, L. (2003). Interventions to reduce HIV/AIDS stigma: what have we learned? *AIDS Educ Prev, 15*(1), 49-69.**

**558. Sengupta, S., Banks, B., Jonas, D., Miles, M. S., & Smith, G. C. (2011). HIV interventions to reduce HIV/AIDS stigma: a systematic review. *AIDS Behav, 15*(6), 1075-1087, doi:10.1007/s10461-010-9847-0.**

**559. Heijnders, M., & Van Der Meij, S. (2006). The fight against stigma: an overview of stigma-reduction strategies and interventions. *Psychol Health Med, 11*(3), 353-363, doi:10.1080/13548500600595327.**

**560. Birbeck, G. L., Chomba, E., Atadzhanov, M., Mbewe, E., & Haworth, A. (2008). Women's experiences living with epilepsy in Zambia. *Am J Trop Med Hyg, 79*(2), 168-172.**

**561. Molina, Y., Choi, S. W., Cella, D., & Rao, D. (2012). The Stigma Scale for Chronic Illnesses 8-Item Version (SSCI-8): Development, Validation and Use Across Neurological Conditions. *Int J Behav Med,* doi:10.1007/s12529-012-9243-4.**