Self-Reported Sleep and Associated Variables In Adults Living with HIV
in Jakarta, Indonesia

BY
HENING PUJASARI
B.S.N. University of Indonesia, Jakarta, Indonesia, 1999
M. Biomed. University of Indonesia, Jakarta, Indonesia, 2006
M. N. University of Melbourne, Melbourne, Australia, 2008

THESIS
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Defense Committee: Mary C. Kapella, Chair and Advisor, Biobehavioral Health Science
Alana D. Steffen, Health Systems Science
David W. Carley, Biobehavioral Health Science
Gabriel J. Culbert, Health Systems Science
Judith A. Levy, Health Policy & Administration
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# TABLE OF CONTENTS

**LIST OF TABLES** ........................................................................................................... v
**LIST OF FIGURES** ........................................................................................................ vi
**LIST OF ABBREVIATIONS** .......................................................................................... vii
**SUMMARY** .................................................................................................................... ix

I. INTRODUCTION ............................................................................................................. 1
   A. Background .................................................................................................................. 1
      1. Prevalence of HIV/AIDS in Indonesia ........................................................................ 1
      2. Pathophysiology of Poor Sleep in HIV ..................................................................... 2
      3. Pathophysiology of Poor Sleep in Substance Use ..................................................... 4
      4. Poor Sleep and Associated Key Variables in HIV ....................................................... 5
         4.1. Poor Sleep and Depression in Adults Living with HIV ........................................... 5
         4.2. Poor Sleep and Anxiety in Adults Living with HIV ............................................... 6
         4.3. Poor Sleep and Fatigue in Adults Living with HIV ................................................ 7
         4.4. Poor Sleep and Pain in Adults Living with HIV ..................................................... 7
         4.5. Poor Sleep and Quality of Life in People Living with HIV .................................... 8
   B. Significance of the Problem ....................................................................................... 9
   C. Dissertation Aims and Framework ............................................................................ 9
      1. Dissertation Aims ...................................................................................................... 9
      2. Theoretical Framework ........................................................................................... 10

II. CHARACTERISTICS AND CORRELATES OF INSOMNIA IN HIV-INFECTED ADULTS RECEIVING ANTIRETROVIRAL THERAPY IN JAKARTA, INDONESIA ........................................ 12
   A. Abstract ..................................................................................................................... 12
   B. Introduction ............................................................................................................... 13
   C. Methods .................................................................................................................... 14
      1. Research Design ....................................................................................................... 14
      2. Study Setting and Participants ................................................................................. 15
      3. Sample Size Estimates ............................................................................................ 15
      4. Survey Measures ..................................................................................................... 16
      5. Study Procedures ..................................................................................................... 18
      6. Statistical Analysis .................................................................................................. 19
   D. Results ....................................................................................................................... 20
1. Demographic and Clinical Characteristics of Study Participants ............................ 20
2. Hierarchical Regression for Correlates of Insomnia ............................... 21
3. Multivariate Logistic Regression for Correlates of Insomnia ............................ 22
E. Discussion ........................................................................................................... 22
F. Limitations and Strengths ................................................................................... 25

III. SELF-REPORTED SLEEP, ASSOCIATED SYMPTOMS, AND QUALITY OF LIFE OF ADULTS LIVING WITH HIV IN JAKARTA, INDONESIA .......................................................... 30
   A. Abstract .......................................................................................................... 30
   B. Introduction .................................................................................................... 31
   C. Methods .......................................................................................................... 33
      1. Research Design ......................................................................................... 33
      2. Study Setting and Participants ..................................................................... 34
      3. Sample Size Estimates .............................................................................. 34
      4. Survey Measures ......................................................................................... 34
      5. Procedure .................................................................................................... 37
      6. Statistical Analysis ....................................................................................... 38
   D. Results ............................................................................................................. 39
      1. Demographic and Clinical Characteristics of Study Participants ................ 39
      2. Bivariate Correlations of Variables of Interest ............................................. 39
      3. Multivariate Linear Regression of Association of Variables of Interest ........ 40
   E. Discussion ........................................................................................................ 40

CITED LITERATURE ................................................................................................. 48
VITA .......................................................................................................................... 55
# LIST OF TABLES

<table>
<thead>
<tr>
<th>TABLE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TABLE I. Bivariate demographic and clinical association with insomnia in HIV-infected adults receiving ART in Jakarta, Indonesia (N=200)</td>
<td>27</td>
</tr>
<tr>
<td>TABLE II. Summary of hierarchical regression for correlates of insomnia (N=172)</td>
<td>28</td>
</tr>
<tr>
<td>TABLE III. Independent and multivariate logistic regression for correlates of insomnia (N=200)</td>
<td>28</td>
</tr>
<tr>
<td>TABLE IV. The characteristics of study participants (N=200)</td>
<td>44</td>
</tr>
<tr>
<td>TABLE V. Correlations among study variables</td>
<td>46</td>
</tr>
<tr>
<td>TABLE VI. Multivariate linear regression with quality of life (N=200, R²= 0.48)</td>
<td>46</td>
</tr>
</tbody>
</table>
### LIST OF FIGURES

<table>
<thead>
<tr>
<th>FIGURE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 1. Study framework for characteristic and correlates of insomnia in HIV</td>
<td>29</td>
</tr>
<tr>
<td>Figure 2. Insomnia in people living with HIV in Jakarta Indonesia</td>
<td>29</td>
</tr>
</tbody>
</table>
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>Acquired Immunodeficiency Syndrome</td>
</tr>
<tr>
<td>AOR</td>
<td>Adjusted Odd Ratio</td>
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<tr>
<td>ART</td>
<td>Antiretroviral Therapy</td>
</tr>
<tr>
<td>ARV</td>
<td>Antiretroviral</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>FACIT</td>
<td>Functional Assessment of Chronic Illness Therapy</td>
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<tr>
<td>HAART</td>
<td>Highly Active Antiretroviral</td>
</tr>
<tr>
<td>HADS-A</td>
<td>Hospital Anxiety and Depression Scale – Anxiety</td>
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<tr>
<td>HADS-D</td>
<td>Hospital Anxiety and Depression Scale – Depression</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>IDU</td>
<td>Injection Drug User</td>
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<tr>
<td>IFN</td>
<td>Interferon</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>ISI</td>
<td>Insomnia Severity Index</td>
</tr>
<tr>
<td>MOH</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>MSM</td>
<td>Men who have Sex with Men</td>
</tr>
<tr>
<td>NGO</td>
<td>Non-Government Organization</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Nonnucleoside Reverse Transcriptase Inhibitor</td>
</tr>
<tr>
<td>NPRS</td>
<td>Numeric Pain Rating Sale</td>
</tr>
<tr>
<td>NS</td>
<td>Not Significant</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
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<tr>
<td>PLH</td>
<td>People Living with HIV</td>
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<td>PSQI</td>
<td>Pittsburg Sleep Quality Index</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
<td>-----------</td>
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<tr>
<td>PWID</td>
<td>People Who Inject Drugs</td>
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<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>RA</td>
<td>Research Assistant</td>
</tr>
<tr>
<td>REM</td>
<td>Rapid Eye Movement</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for Social Science</td>
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<tr>
<td>SRS</td>
<td>Self Rating Scale</td>
</tr>
<tr>
<td>STI</td>
<td>Sexually Transmitted Infection</td>
</tr>
<tr>
<td>TCU</td>
<td>Texas Christian University</td>
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<tr>
<td>UCSF SMT</td>
<td>University of California San Francisco Symptom Management Theory</td>
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<tr>
<td>UNAIDS</td>
<td>Joint United Nations program on HIV/AIDS</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<td>WHOQoL</td>
<td>World Health Organization Quality of Life</td>
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</tbody>
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SUMMARY

The purpose of this study was to determine the correlates of self-reported sleep and to understand the impact of sleep on quality of life among adults living with HIV in Indonesia. Prior studies mainly from high-income countries provide insights into the importance of sleep in people living with HIV (PLH). Current evidence indicates that poor sleep has negative consequences on PLH, including decreased adherence to antiretroviral therapy (ART) and diminished quality of life. Addressing factors associated with poor sleep in PLH is vital to enhance quality of life for PLH.

This dissertation is presented in the form of two manuscripts. The first manuscript focuses on characteristics and correlates of insomnia while the second examines association between self-reported sleep, other symptoms, and quality of life. Together, the results of the two manuscripts highlight the characteristics and the variables that are associated with poor sleep in this population. This dissertation study represents one of the first studies of sleep in persons living with HIV (PLH) conducted in a lower middle-income, Muslim majority, Asian country. In this population of HIV-infected and mostly drug-dependent adults receiving ART, almost two-thirds (67%) of them indicated poor sleep according to the Pittsburg Sleep Quality Index (PSQI) and one-third (33.5%) had Insomnia Severity Index (ISI) scores indicating clinically significant insomnia, which by itself impacts daytime functioning, quality of life, and may contribute to suboptimal ART adherence in this population. It was noted that when PLH with and without insomnia were compared, insomnia significantly differed by level of ART adherence, drug use, opioid use, anxiety, depression, pain, fatigue, sleep environment, and religious practice. Our data support the idea that HIV infection potentially predisposes or precipitates insomnia due to the psychosocial stress associated with it.

Using hierarchical regression analysis, and guided by The University of California San Francisco Symptom Management Theory, we found that compared with variables under
person and environment domains, the most significant correlates of insomnia were variables under health/status dimension (anxiety, fatigue, pain) that uniquely explained around one-third of the variance in insomnia. After adjusting for other covariates, insomnia was positively associated with anxiety, fatigue, and pain, and negatively associated with ART adherence and Islamic practice.

We also examined the association of a self-reported and important symptom outcome; quality of life. Our key findings were that adjusted for gender, level of education, drug/alcohol use, and ART adherence, quality of life was negatively associated with fatigue, self-reported sleep (insomnia), and methadone treatment.

Our results suggest that interventions that focus on helping adults living with HIV in the Indonesian context would need to assist patients to reduce levels of fatigue and insomnia. Future research is necessary to explore how PLH on methadone treatment could be assisted to deal with treatment-associated issues that affect quality of life.
I. INTRODUCTION

This dissertation has three chapters that examine the characteristic self-reported sleep and associated variables in adults living with HIV in Jakarta, Indonesia. Chapter One introduces background, problem gap, study aims, and theoretical framework. Chapter Two includes the first manuscript that focuses on characteristics and correlates of insomnia. Chapter Three includes the second manuscript that examines associations between self-reported sleep, other symptoms, and quality of life.

A. Background

1. Prevalence of HIV/AIDS in Indonesia

Until the late 1990s, human immunodeficiency virus (HIV) prevalence in Indonesia was estimated to be less than 1% among traditional at-risk populations including injected drug users (IDUs), commercial sex workers, and men who have sex with men (MSM) [1]. Beginning in 1998, surveillance reports revealed a growing number of acquired immunodeficiency syndrome (AIDS) cases in the provinces and along its international seaports. By 2003, HIV in Indonesia had reached what the World Health Organization (WHO) refers to as the “concentrated stage” – all the factors were present for a rapidly spreading epidemic [1]. These include an extensive sex industry, limited capacity to detect and treat HIV/sexually transmitted infections (STIs), a highly mobile population that can facilitate spread of the virus, an explosion in injection drug use, and increasingly high-risk social conditions for HIV exacerbated by massive economic instability and political disruption [2, 3]. With its large population, although HIV prevalence is low, it is one of the fastest growing epidemics in Asian countries [3-7].

By 2009, 333,200 Indonesians were estimated to be living with HIV, 25% of whom were women [8]. Apart from Papua province, HIV is concentrated in particular key populations. Most infections continued to occur in high-risk populations, particularly IDUs, sex workers, and MSM. More than half of IDUs (52%) were estimated to have contracted the virus, with a slightly higher
prevalence among female injectors [8]. Waria (transgender) individuals were also identified as a highly vulnerable group with rates around 24%. Prisoners in Indonesia, most of whom are serving time for drug-related charges, were found to be highly susceptible to HIV due to the convergence of drug injection, prison tattooing, and same sex practices during incarceration [9]. Meanwhile, a generalized epidemic emerged in Indonesian-Papua New Guinea where HIV prevalence was estimated to be 15 times higher than the national average [10].

Largely due to lack of understanding the symptoms of the disease and the high social stigma attached to it, only 5-10% of people with HIV/AIDS were diagnosed and treated [1]. In 2014, the United Nations program on HIV/AIDS (UNAIDS) considered Indonesia as underperforming in its response to HIV/AIDS[1] [2]. New cases increased by 47% since 2005. Currently, deaths from AIDS are still high since only 8% of PLH receive treatment with ART. Data from the Ministry of Health (MOH), from 2005 to September 2015, showed a significant increase of cases compared to previous years. There is also a trend of transition of cases from a concentrated to a more generalized HIV epidemic due to the sexual behavior of key populations [11]. New HIV cases are projected to increase at a higher rate in men than women due to HIV incidence among MSM. However, female partners of men who inject drugs, men who have sex with female sex workers, and MSM are considered at risk for HIV and remain undiagnosed until they develop symptoms or lose a child due to HIV/AIDS [4]. By 2014, the male-to-female ratio of cumulative AIDS cases in Indonesia was 1.8:1 [11].

2. Pathophysiology of Poor Sleep in HIV
Poor sleep is among the first symptoms of HIV infection [12]. Poor sleep is defined here as difficulty falling asleep or staying asleep, awakening too early, or unrefreshing sleep in combination with at least one daytime symptom such as sleepiness or irritability [13]. Poor sleep becomes a universal complaint in the later stages of HIV infection which might suggest that HIV itself affects biological sleep centers [14]. The sleep changes that occur in HIV infection have been quantified in several studies employing polysomnography; however, the data are
conflicting. Previous studies indicated that infection by HIV changes the normal cycle of rapid eye movement (REM) and non-REM and results in non-restorative sleep; advanced stage of the disease is associated with disruption of sleep patterns [15, 16]. The pathophysiology of poor sleep in HIV is still unclear [17]. The most plausible potential mechanisms of poor sleep in HIV along the course of illness include HIV-associated neural defects, chronic sadness, and HIV medication effects [14].

There are two key characteristics of HIV infection in the central nervous system (CNS): 1) *cumulative* and 2) involving both *direct* and *indirect* effects. HIV does not appear to infect neurons specifically. Instead, the virus infects peripheral macrophages and microglia. These immune cells then migrate to CNS across the blood-brain barriers. As many current highly active antiretroviral (HAART) regimens fail to reach the CNS, these infected cells become viral reservoirs. The gradual *accumulation* of CNS viral load may explain the tendency of poor sleep with duration of infection. The other nature of CNS defect by HIV is *direct* and *indirect*. The release of neurotoxins by HIV-infected cells can *directly* destroy neurons and synapses. Indirectly, CNS infection activates inflammatory mediators – cytokines, chemokines, and more macrophages. The combination of both neurotoxins and inflammatory mediators causes intensifying neural damages, especially dopaminergic and glutamatergic neurons [14], both of which appear to be involved in regulating sleep process [18].

Another potential factor related to poor sleep in HIV is the side effect of certain types of ART, particularly the class of non-nucleoside reverse transcriptase inhibitors (NNRTI). Although it could be difficult to distinguish the drug toxicity from neural defects by the virus and immune activation [19], previous studies have reported poor sleep as an important side effect of certain ART medications [20-23]. Efavirenz is the most common ART associated with CNS toxicity, causing poor sleep, irritability and vivid dreams [24]. The medication’s side effect on sleep, however, appeared to be mild [25] and decrease with time [26].
Finally, psychiatric symptoms including depression, anxiety and stress have been identified as factors associated with poor sleep among HIV-seropositive individuals. Those factors are not specific to the HIV population, but may be exacerbated in persons with chronic illness and have implications for potential mechanisms of poor sleep in this population [14].

Clarification of the relationship between self-reported sleep and HIV/AIDS may lead to interventions and self-management strategies to address poor sleep. More studies are required to reveal process associated with HIV infection and disturbed sleep.

3. Pathophysiology of Poor Sleep in Substance Use
Poor sleep is associated with acute and chronic use of alcohol, cannabis, cocaine, and opiate use [27]. Substance use affects neurotransmitter systems that regulate the sleep-wake system [28]. Although poor sleep associated with use and abstinence from addictive substances is widely recognized, knowledge about its mechanism is lacking [29]. A recent study highlights the interaction between substance use and poor sleep. The poor sleep prevalence rate of opiate addicts under methadone therapy was high [30]. The association between poor sleep and substances use appears to be bidirectional. The side effects of addiction or withdrawal might result in poor sleep and poor sleep predicted substance use [31]. Pasch et al found that cigarette use and weekend sleep were bi-directionally related as were marijuana use and total sleep [32].

In general, the evidence points to chronic alterations in sleep from chronic use of addictive substances that may be distinct from the acute effects of those substances. Interestingly, the effects of chronic use on sleep are similar among both CNS stimulants and depressants. Decreased sleep time, increased sleep latency and wake time after sleep onset, and deficiency in slow-wave sleep generation appear to be common to the chronic use of alcohol, cocaine, cannabis, and opiates [28, 33].

Substance use can cause behavioral or neurobiological sensitization, intensifying the rewarding effects. With frequent administration, down regulation of these systems may lead to a
decrease in the impact of the substance on the reward circuits of the brain, leading the abuser to dependence. Substance use can alter the homeostatic balance of neurotransmitters systems, such as acetylcholine, GABA, dopamine, glutamate, norepinephrine, and the orexin systems; a neuropeptide that regulates arousal, wakefulness, and appetite. These neurochemical changes may lead to the need to increase the dose of the drug to achieve the same effect and withdrawal, which can further contribute to the development of dependence. Many of the same neurotransmitter systems affected by substance use are involved in the regulation of sleep-wake systems. As a result, poor sleep and sleep dysregulation may result at various stages of substance use or withdrawal [18, 28].

4. **Poor Sleep and Associated Key Variables in HIV**
Several variables have been found to be significantly associated with sleep problems in PLH. In general, variables are categorized into person; health/illness; environment; and symptom outcome variables. From the most studied to the least, person variables include gender, education, employment, having a partner, and ethnicity [34], risk behavior, substance use, tobacco-smoking, and history of incarceration [35-39]. Health/illness variables include depression, anxiety, stress, anxiety sensitivity, and suicidal ideation [40-42], fatigue, inflammation markers, pain, CD4 cell count, viral load, disease stage, symptom severity, diagnosis duration, dopamine level, oxytocin level, Efavirenz-based regimen, and waist size [43-48]. Symptom outcome variables include quality of life, medication adherence, daytime sleepiness, cognitive functioning, and daytime functioning [15, 16, 35, 36, 38]. Environment variables include social support [46].

4.1. **Poor Sleep and Depression in Adults Living with HIV**
Depression is a common response to HIV/AIDS diagnosis. Studies show that people who are infected with HIV are more likely to develop depression than the general population [49]. In the general population, sleep quality is strongly associated with parameters of mental health issues, mainly depression and anxiety, [50] with the most plausible mechanism being that
elevated cortisol levels during episodes of depression and anxiety decrease slow-wave sleep and increase the number of intermittent awakenings. Poor sleep is experienced by 70% of depressed individuals [51]. Not surprisingly, depression is among other variables that have been widely studied in relation to poor sleep in adults living with HIV. To date, literature has demonstrated that depression is the major key variable in poor sleep among HIV-infected individuals [52]. In addition, the relationship between depression and sleep is known to be bidirectional [53].

Five recent multivariable studies on sleep in the HIV population consistently found that depression predicted poor sleep in HIV infected persons. Four of these studies were conducted in different settings and involved different sub-populations. A study by Saberi et al involved representative sample size (N=2845) on ART patients in four cities in the U.S. [54]. Crum-Cianflone et al involved 193 early-treated U.S. military personnel [53]. In the Jean-Louis et al study, participants were 1682 women from six cities in the U.S. [52]. Oshinaike et al, involved 300 outpatients in an African context, Nigeria [22]. And finally, Allavena et al. conducted a study on 1354 outpatients in France [21].

4.2. Poor Sleep and Anxiety in Adults Living with HIV
Anxiety is highly prevalent in HIV positive individuals. It is reported that 47% of the population experiences anxiety and that it can pre-exist or occur during HIV infection [55]. Anxiety is the second major psychological variable associated with poor sleep in HIV [53]. This is through a mechanism where sleep diminishes cortical arousal, anxiety intensifies cortical and peripheral arousals, and increased arousal disturbs sleep initiation or maintenance. Patients with anxiety disorders have delayed sleep onset and reduced total sleep time [56]. Using Beck Anxiety Inventory, Junqueira et al measured anxiety among 30 females with HIV/AIDS and 30 female controls. They found that poor sleep measured using PSQI was strongly associated with anxiety level, thus the higher the anxiety score, the higher the poor sleep score [42]. Dabaghzadeh et al found a significant association (r=0.531, p=0.0001) between sleep quality
(PSQI) and anxiety (Hamilton Anxiety Rating Scale) [40]. Gamaldo et al found that of the 25 HIV positive participants, their poor sleep severity scores (Insomnia Severity Index) were correlated with anxiety symptoms (State-trait Anxiety) [16].

4.3. Poor Sleep and Fatigue in Adults Living with HIV
Fatigue is one of the most prevalent complaints among adults living with HIV [57], and ranges from 17%-60% in people with HIV, and from 43%-85% in people with AIDS [58]. Pathogenesis of fatigue remains unclear. Fatigue has been found to have a strong association with poor sleep, with the current hypothesized mechanism suggesting that inflammatory pathways may be involved in the production of fatigue and poor sleep. Elevated levels of cytokines, including interleukin 6 (IL-6), IL-1, and Interferon (IFN)-alpha have been found to be associated with both fatigue and poor sleep [59].

Low et al conducted a study to test whether insomnia severity (Insomnia Severity Index) is correlated with increased fatigue (Piper Fatigue Scale) in 57 ambulatory HIV-seropositive patients. They found a positive association between insomnia and fatigue [60]. The Salahuddin et al study used PSQI to measure nighttime sleep quality and the HIV-Related Fatigue Scale to measure several aspects of fatigue. They found that poor nighttime sleep was significantly associated with one aspect of fatigue-fatigue intensity (r=0.46, p<0.05) [36]. The Gamaldo et al study measured fatigue using the Fatigue Severity Scale and found that among PLH, Insomnia severity scores (ISI) were correlated with fatigue [16]. Marion et al conducted a study to investigate the interplay between distress (Epidemiologic Studies of Depression), sleep difficulty (PSQI), and fatigue (Fatigue Symptom Inventory). They found that greater distress was associated with greater fatigue and greater sleep difficulty [41].

4.4. Poor Sleep and Pain in Adults Living with HIV
Pain is one of the most common symptoms in people with HIV infection at all stages of the disease. In a systematic review, which included 61 studies, prevalence of pain in PLH was 54% with the reported pain intensity ranging from moderate-to-severe. Pain was reported in
multiple pain sites, suggesting that there are several differing pathological processes simultaneously contributing to pain [61].

Pain has been found to be associated with poor sleep, awakenings, and shorter sleep time for those with chronic diseases. Axen et al conducted a prospective observational study of 233 patients in which acute and persistent pain were used to identify the prevalence of poor sleep, the correlation of pain, and poor sleep. It was found that poor sleep was reported by 67% of the sample. Measures of pain and poor sleep were significantly correlated. Compared to being pain free, the risk of reporting poor sleep after experiencing pain the previous week was significantly increased. Pain and sleep measures were significantly correlated, and there was an increased risk of reporting poor sleep after experiencing pain [62].

A study by Sandoval et al indicated that about 50% of HIV infected participants experienced and ranked increases in pain and poor sleep among the top four symptoms associated with people living with HIV infection. Of 46 HIV infected with neuropathic pain individuals, it was found that the pain experience was moderate to severe and significantly associated with poor sleep [63].

**4.5. Poor Sleep and Quality of Life in People Living with HIV**

Quality of Life (QoL) is a multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning. QoL is an important variable that can predict population health, life expectancy, and causes of death [64]. A related concept of QoL is well-being, which measures the positive aspects of life, such as positive feelings and life satisfaction. QoL and well-being are used to measure the effects of chronic illness, treatments, and short- and long-term disabilities [65]. In general and in specific chronic disease populations, the association between sleep and quality of life or well-being have been extensively studied and confirmed to be associated. It is apparent that few studies have been conducted in the HIV population that established this association. A study by Phillips et al examined the associations of sleep quality (measured using PSQI) and QoL (measured using Short-Form Health Survey,
SF-36) in 144 HIV-infected African-American women. Multiple regression analysis indicated that sleep quality was associated with QoL, independent of the individual's stage of illness [66].

A growing body of evidence demonstrates a significant relationship between spirituality and health. HIV-infected individuals often find new meaning and purpose for their lives while establishing new connections and strengthening old ones. A descriptive, correlational study by Phillips et al examined the relationships among spiritual well-being, sleep quality, and health status in 107 HIV-infected men and women in the U.S. Spiritual well-being was found to be a significant factor related to both sleep quality and mental and physical health status [67].

B. **Significance of the Problem**

Poor sleep in people living with HIV (PLH) is still largely unevaluated and untreated [8], despite study findings suggesting that treatment for poor sleep should be a primary concern in the treatment of HIV infection as a means for achieving treatment goals and improving quality of life [24]. In addition, literature provides more evidence regarding the relevance of assessing sleep as part of the clinical assessment of patients with chronic illnesses, including HIV, and it should be recognized and promptly implemented by healthcare professionals [68]. In view of the extremely common problem of poor sleep in HIV-infected people, the present sleep aids and behavioral treatments in HIV treatment settings are clearly inadequate [8]. While context-specific sleep interventions are necessary, currently, there is no literature in the Indonesian context that characterizes sleep to be used for designing them. The purpose of this dissertation study was to examine the characteristics of self-reported sleep, its associated variables, and quality of life of PLH in Indonesia.

C. **Dissertation Aims and Framework**

1. **Dissertation Aims**

Using the University of California San Francisco Symptom Management Theory (UCSF SMT) [69] as a guide, the study provides an empirical basis for developing and testing interventions to promote good sleep in the target population.
The specific aims and research questions in this study were as follows:

Aim 1: To characterize self-reported sleep of PLH receiving ART in Jakarta, Indonesia.

Aim 2: To examine relationships among self-reported sleep, person, health/illness, environment, and quality of life variables in adults living with HIV.

A major goal of HIV care, in addition to viral suppression, is effective symptom management meant to eliminate or minimize the impact of disease in order to enhance optimal health state and quality of life. Poor sleep is one of the common symptoms in PLH that can diminish quality of life. This study characterized self-reported sleep and generated data useful in designing interventions for PLH in Indonesia. These data will be useful in raising awareness of sleep problems in PLH leading to policy development to promote sleep in HIV care.

2. Theoretical Framework

This dissertation was guided by the UCSF SMT [69]. The SMT has three major components; symptom experience, symptom management, and symptom outcomes. These components simultaneously interact (see Figure 1) and are placed within the context of the domains of: person, health/illness, and environment. Among the three SMT major components, symptom experience is illustrated as the beginning of the symptom management process. This component consists of three aspects; the individual’s perception, evaluation, and response to a symptom. These relationships are acknowledged to possibly occur repetitively and or simultaneously [70]. The second component, symptom management strategies, are described as the what, where, why, how much, to whom, and how; which guide the clinician or investigator in selecting appropriate intervention strategies and are intended to prevent, delay, or minimize the symptom experience. The third component is the outcomes and symptom status. This component includes seven aspects that the individual may experience as the result of the symptom experience and/or symptom management strategies. These aspects are functional status, emotional status, self-care, costs, quality of life, morbidity and comorbidity, and mortality [69].
This study focused on two of the three components of SMT, symptom experience and outcome. Self-reported sleep was the central component. In this study the person domain included gender, substance use, and ART adherence. The health/illness domain comprised of variables that are unique to the health or illness state [69]. In this study, health/illness domain included variables anxiety, depression, fatigue, and pain. The third domain, the environment, involves physical, cultural, and social variables representing the conditions in which a symptom occurs. In this study, environment domain contains sleep environment and religious practice. Since the focus of this study was to characterize self-reported sleep and because one of the main goals of HIV care is QoL, QoL was considered a most important outcome measure in the study. Therefore, the relationship of poor sleep and QoL was explored.
II. CHARACTERISTICS AND CORRELATES OF INSOMNIA IN HIV-INFECTED ADULTS RECEIVING ANTIRETROVIRAL THERAPY IN JAKARTA, INDONESIA

A. Abstract

Background: Difficulty falling asleep, staying asleep and poor sleep quality, also known as insomnia, is one of the most common symptom complaints in people living with HIV (PLH) at every disease stage, and is associated with poor adherence to antiretroviral therapy (ART). Substance use comorbidities and medications to treat opioid addiction may also influence sleep patterns. In Indonesia, HIV prevalence among people who inject drugs (PWID) has remained consistently high (>50%), yet very little information exists about insomnia in this population. Aims: This study examined the characteristics and correlates of insomnia in PLH in Indonesia. Methods: From May-September 2016, a convenience sample of 200 PLH was recruited from a community organization serving PWID in Jakarta, Indonesia. Eligible participants were ≥18 years of age, HIV-infected, receiving ART for at least 3 months, and medically stable (Karnofsky score >40). Interviewer-administered questionnaires assessed insomnia, using the Insomnia Severity Index (ISI); substance use within the past year; ART adherence within the past 1 month; anxiety, depression, pain, fatigue; and sleep environment within the past one week. Bivariate and multivariate associations with insomnia (ISI score >10) were examined. Results: One-third of participants (33.5%) had ISI scores indicating insomnia. After adjusting for gender and substance use, clinically significant insomnia was positively associated with anxiety (AOR=1.15, 95%CI=1.01-1.29, p=0.03), pain (AOR=1.17, 95%CI = 1.02-1.36, p = 0.03), fatigue (AOR=1.09, 95% CI=1.03-1.16, p = 0.00), and negatively associated with ART adherence (AOR=0.62, 95% CI=0.42-0.90, p=0.01). Conclusion: Insomnia is a common health problem in PLH. Screening for insomnia and its related conditions during HIV care is indicated.
B. Introduction

Sleep serves to promote physical and mental restoration during the wakeful period. Poor sleep can cause problems in all aspects of life and may affect a patient’s ability to recover from illness [71]. In the context of chronic illnesses such as HIV infection, achieving the balance of sleep and wakefulness can be difficult, but crucial [72]. Unfortunately, insomnia, defined as difficulty falling asleep, difficulty staying asleep, awakening too early, or unrefreshing sleep in combination with at least one daytime symptom such as sleepiness or irritability [13]; is highly prevalent among people living with HIV (PLH) at every disease stage [22]. A particular concern is that insomnia is associated with decreased adherence to antiretroviral therapy (ART) [38], which, in turn, can lead to treatment failure (i.e. loss of virologic control), and development of drug-resistant strains of HIV [73].

Although insomnia in PLH is well documented [73], the characteristics and correlates of insomnia in PLH have not yet been fully elucidated [14]. Many factors can contribute to insomnia, even in healthy individuals, and PLH are faced with more complex and unique situations that specifically affect their ability to sleep normally [74]. Untreated mental illness or substance use disorders, which are more common in PLH compared to the general population, may aggravate insomnia in PLH [8]. There is variability of correlates of insomnia in particular contexts. From the most commonly studied to the least, the correlates of poor sleep include gender, education, employment [34], not a having a partner [48] and substance use [75]. Correlates of poor sleep related to health/illness include depression, anxiety [40, 42], fatigue [16, 76], inflammation markers [44, 77], and pain [45]. Correlates of insomnia related to outcome variables include quality of life, daytime functioning [16], medication adherence [38] cognitive functioning [35]. The environment variable correlated to insomnia was social support [46].

Although numerous studies have examined insomnia in PLH, few have occurred in Asian countries and none have occurred in Indonesia. The most recent meta-analysis aimed
to estimate the pooled prevalence of insomnia in the HIV population found that the insomnia differed by region [73]. Thus there is regional disparity in sleep and sleep problems [78]. There were insufficient studies conducted in Asian countries.

HIV incidence and mortality are increasing in Indonesia, despite global reductions [79]. Jakarta has the highest number of PLH in the country. HIV is primarily concentrated and transmitted among people who inject drugs (PWID) [80], although recent evidence suggests increasing sexual transmission from PWID to their partners [81]. For PWID, physical, psychological, and social dysfunctions can generate additional stressors of living with HIV [82] that can exacerbate insomnia. In addition, Indonesia is different from most of its neighbors given that it is a geographically and culturally diverse country with a large Muslim population [83]. It is therefore likely that sleep patterns and its associated variables in PLH could be unique in this context given that cultural beliefs affect sleep activity and how people perceive their sleep [84]. Religious practices such as prayer calls during early morning may influence sleep patterns and quality [67] and have not been identified in other settings. Environment and religious practices may contribute to ability to sleep among Indonesian PLH.

Using the University of California San Francisco Symptom Management Theory (UCSF SMT) [69] as a guide, we examined: the characteristics and correlates of insomnia in adults living with HIV in Jakarta, Indonesia. The SMT has three major components; symptom experience, symptom management, and symptom outcomes. These components are placed within the context of the domains of nursing science: person, environment, and health/illness.

C. Methods

1. Research Design
In this cross-sectional study, a convenience sample of PLH (N=200) recruited from a community organization serving PWID and HIV care in Jakarta, completed paper surveys measuring sleep, health symptoms, adherence to ART, and substance use. Ethical approval was obtained from two institutional review boards (IRBs) at the University of Illinois at Chicago
and Universitas Indonesia. The study also received approval from the community organization where data was collected. Written informed consent was obtained prior to study procedures.

2. **Study Setting and Participants**

   Key at-risk populations in Indonesia are concentrated in cities, and 40% of PLH are living in just 4 cities, including Jakarta, where over half (56.4%) of PWID are HIV-infected. Non-governmental organizations (NGO’s) have played a vital role in Indonesia’s multi-sector response to the HIV epidemic, and especially those providing harm reduction services (e.g. needle-syringe exchange), HIV testing, and linkage to care for PWID [85]. Many first-line antiretroviral (ART) drugs are manufactured domestically and, since 2004, provided to patients free of cost. ART has, until recently, been prioritized for patients with advanced HIV (WHO clinical stage 3 or 4) but the Ministry of Health made efforts to conform to international guidelines recommending treatment for all PLH regardless of CD4 cell count [10].

   This study was conducted at KIOS Atma Jaya, a community-based organization located in West Jakarta, established in 2002 as an outreach hub providing HIV prevention and harm reduction services to over 3,000 PWID across 27 neighborhoods. Staff members including physicians, peer educators and outreach specialists provide harm reduction services, case management, and referrals for drug treatment, HIV testing, and medical care. Eligible participants were 18 years or older, HIV-infected by self-report, receiving ART for at least 3 months (confirmed by drug prescription card), and provided informed consent. There was no potential participant with a Karnofsky performance score ≤ 40% (severely disabled or likely to be admitted to the hospital) therefore none of them were excluded [86].

3. **Sample Size Estimates**

   Sample size was determined based on power analysis for multiple regression using G*Power software version 3.1.9.2. In this study, the total number of tested correlates was nine; gender, opioid use, ART adherence, anxiety, depression, pain, fatigue, sleep environment, and religious practice. Using alpha level of 0.05, effect size of 0.05, and power of 0.85
(recommended power above 0.80), the minimum sample size required is 146. In this study the sample was increased to 200 in case of missing data. Considering the feasibility of conducting the study, the sample size of 200 was the ideal achievable number. The effect size ($f^2=0.05$) was comparable to an $R^2$ increase of 5% for an individual variable and was considered useful in detecting small (or larger) correlates of sleep quality. In comparison, a previous study indicated both fatigue and pain explained by 0.34 of variance in sleep quality among HIV individuals [74].

4. **Survey Measures**

Instruments that tested for their validity in Indonesian context were used to measure all key variables, except sleep environment. Official permission to use the tools was sought from the instrument developers. **Insomnia** was assessed using the Insomnia Severity Index (ISI) [87], which includes seven Likert-type items measuring sleep onset, ability to stay asleep, early morning wakening, sleep satisfaction, and sleep problems that interfere with daytime activities, are noticed by others, or distressful [88]. During the ISI development, procedures to establish its validity were face and content validity. ISI has been found to be correlated with sleep diaries, polysomnography, and interviews. The reliability tests included test-retest and internal consistency (Cronbach’s $\alpha = 0.91$) [89]. Possible total scores ranged from 0 to 28, with total score $>10$ indicating clinically significant insomnia [87]. ISI mean scores were also categorized as “clinically-non-significant” ($\leq7$); “sub-threshold” (8-14); “moderate” (15-21), or “severe” (22-28) [90]. Cronbach’s alphas for the ISI in this study was high ($\alpha=0.88$).

**Drug and alcohol use** was assessed for the 30 days before study enrollment using the Texas Christian University (TCU) drug screen II, previously adapted for Indonesia [91]. The adapted version of the TCU II includes 15 items measuring type, route, and frequency of drug use, recurring consequences for drug use, and withdrawal symptoms. A single question was used to assess current methadone use.
**HIV Treatment factors** included year of HIV diagnosis and months receiving ART. **ART adherence** was measured with the single-item self-rating scale (SRSI) that uses qualitative adjectives arranged in a 5-point Likert-type scale, from “very poor” to “excellent” to describe medication adherence during the last 30 days. This single item measure is easy to administer, not prone to ceiling effects, and as good as or better than other adherence measures at predicting adherence-related clinical outcomes such as HIV viral load and CD4+ cell count [92, 93].

**Anxiety and depression** were measured using the Hospital Anxiety and Depression Scale (HADS), a 14-item self-report questionnaire that assesses psychological distress in people with medical illness, with two subscales measuring anxiety (HADS-A) and depressive symptoms (HADS-D). Respondents were asked to select which of four options (rated 0-3) best describe their feelings during the previous week [94]. The range was from 0-21. A score ≥ 8 on either subscale indicates “anxiety” or “depression” [95]. Validity using confirmatory factor analysis in the Indonesian setting yielded two factors in accordance with HADS-A and HADS-D except item 3 & 4. They are also found to be reliable in Indonesia, with internal consistency: Cronbach’s alpha 0.77 and 0.74 respectively [96]. In this study, Cronbach’s alphas for the HADS-A, HADS-D and HADS total were 0.78, 0.50, and 0.74 respectively.

**Pain** was assessed using Numeric Pain Rating Scale (NPRS), which measures the pain severity and is often used to evaluate treatment response. Participants were asked to rate their pain in the last seven days, on a numeric scale from “0” no pain at all to “10” worst pain imaginable. High test–retest reliability has been observed in both literate and illiterate patients (r = 0.96 and 0.95, respectively) [97].

**Fatigue** was measured using the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue Scale), a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function. The FACIT-Fatigue Scale uses a 5-point Likert-type scale from 0 “Not at all” to 4 “Very Much.” Two items were reverse scored.
Possible scores range from 0-52, with a score >30 indicating “severe fatigue” [98]. Subsequent to its development, it has been employed in over 150 published studies including over 40,000 people from different chronic illnesses including HIV/AIDS. In all cases, the FACIT-Fatigue Scale has been found to be reliable and valid [99]. Cronbach’s alpha for FACIT-Fatigue Scale in this study was high (α=0.90).

Sleep environment was assessed by a sleep environment questionnaire. A 25-item Likert-type survey was developed specifically for the Jakarta urban setting to assess environmental factors such as noise; temperature, insects, mattress firmness and number of other persons sharing the bed. Participants were asked to respond to questions, for example: “During the past week how often have you had trouble sleeping because of the street noise,” using the following Likert scale: never, rarely, sometimes, often, and always. Scores were calculated by summing all individual item scores. Possible total scores ranged from 25 to 125 with higher scores indicating a less conducive sleep environment. Cronbach’s alpha in this study was high (α=0.86).

Religious practice (assessed among Muslim participants only), was measured using the Islamic Involvement Questionnaire. The measure, which assesses religious behavior, consists of 14 items, and use a five-point Likert scale ranging from strongly disagree = 1 to strongly agree = 5. Scores were determined by summing all items in the respective subscale (14-70). Higher scores reflect greater religious practice, with a score >45 indicating high religious practice [100]. Cronbach’s alpha for the measure in our study was 0.81.

Demographics measured included: age, gender, education level, relationship status, employment, religion, and ethnicity.

5. Study Procedures
All data was collected by two researchers, including the Principal Investigator (PI) and a trained Research Assistant (RA), during a single study visit. Study visits occurred at a community organization, KIOS Atma Jaya, where participants were recruited. To ensure
consistency in data collection procedures, the principal investigator debriefed research assistants each day that data was collected.

Flyers were displayed at KIOS Atma Jaya that contained the researchers’ phone number; 2) interested potential participants called the researcher or talked to the officer of the organization; 3) a date and time for meeting the potential subjects was set when they contacted the researcher; 4) upon meeting the potential subjects, the researcher screened the potential participants using the Karnofsky Scale; 4) the researcher provided free and informed consent; and 5) the researcher interviewed the participants. Participants were compensated for their time and transport costs, and they received a total of $10.

6. Statistical Analysis
Data were analyzed using the IBM SPSS Statistics version 23. All continuous variables were checked for normality of distribution by looking at kurtosis and skewness, visual inspection of histograms, and Q–Q plots. No outliers were found. There were no missing data and no variables were required to be transformed. Descriptive statistics, means and standard deviations for continuous, and percentages for categorical variables were calculated for all measures, including demographic characteristics.

In order to characterize insomnia, descriptive statistics were used. To identify correlates of insomnia, correlations and hierarchical regression models using enter method were conducted using a sub-sample of Muslim participants (N=172) who were assessed on their religious practice. Variable selection was based on the SMT, the empirical data and the statistical significance in bivariate analysis. Prior to conducting a hierarchical multiple regression, the relevant assumptions of this statistical analysis were tested. A sample size of 172 was adequate given nine independent variables to be included in the analysis. The assumption of singularity was also met as the independent variables were not a combination of various independent variables. An examination of collinearity revealed that no independent variables were highly correlated (r>0.7). The collinearity statistics (i.e., Tolerance and VIF)
were all within accepted limits, and the assumption of multicollinearity was considered to have been met [101].

A three step hierarchical multiple regression involving three blocks reflecting the three dimensions of SMT (person, health/illness, and environment) was conducted with insomnia total score as the dependent variable (Figure 1). Variables under person dimension of SMT (gender, opioid use, and ART adherence) were entered at step one of the regression. Variables under health/illness dimension (anxiety, depression, pain, and fatigue) were entered at step two. Variables under environmental dimension (sleep environment and Islamic practice) were entered at step three. The three step analysis resulted in three models (Model I, II, and III) summarized in TABLE II.

Logistic regression was conducted that included all participants (N=200) to establish correlates of insomnia. The ISI total score for insomnia (cut off >10 for clinically significant insomnia) was the dependent variable. In the logistic regression, the independent variables were the same as in the linear regression Model III, except that religious practice was excluded since the measure used was for Islamic practice of Muslim participants only. Significance was set at p< 0.01 and < 0.05 for all analyses.

D. Results

1. Demographic and Clinical Characteristics of Study Participants
Characteristics of study participants are summarized in TABLE I. Participants were 35 years of age on average, mostly male (78.5%), and married or in a relationship (59.5%). Most (70%) had completed high school and were employed (63.5%). Participants were HIV diagnosed for 6.9 years on average (range: 0-19 years) and had been receiving ART for an average 4.5 years (range: 3 months - 17 years) at the time of the study. Almost 50% of Muslim participants did not fully practice their religion.

On average, the participants experienced sub-threshold insomnia. The mean of Insomnia Severity Index scores was ≤10 (8.7 ± 5.83). Using the ISI original cut off scores
absence of insomnia (0-7); sub-threshold insomnia (8-14); moderate insomnia (15-21); and severe insomnia (22-28), it was found that more than 50\% of the participants indicated sub-threshold to severe insomnia (Figure 2). The ISI >10 cut off scores revealed that one-third (33.5\%) of participants had clinically significant insomnia. The mean scores of anxiety (6.0 ± 3.8, cut off >7), depression (6.3 ± 3.2, cut off>7), pain (2.6 ± 2.7, mild (1-3), and fatigue (16.5 ± 9.0, cut off>30), indicated that on average, the participants experienced mild anxiety, depression, pain, and fatigue (TABLE I).

Mean self-reported ART adherence among participants without insomnia (4.5 ± 1.0, between “good” and “very good”) was significantly higher than among those within clinically-significant insomnia (3.9 ± 1.0, less than “good”, $p<0.001$). About half of the participants (54.5\%) reported active substance use with drugs or alcohol, and a quarter (23\%) had used illicit opioids within the past year. About half of the participants (55.5\%) were currently receiving methadone. The proportion of participants with insomnia reporting alcohol and drug use (68.7\%) or opioid use (37.3\%) was significantly higher than among participants without insomnia (47.4\% and 15.8\% respectively, $p<0.001$). Among participants with clinically-significant insomnia, mean scores for anxiety (8.4 ± 3.4), and depression (7.9 ± 2.8), were above the normal range (>7) and significantly higher ($p<0.001$) than among participants without insomnia). Likewise, mean pain (4.1 ± 2.9), and fatigue (22.9 ± 8.3) scores were also elevated in participants with insomnia compared to those without (1.8 ± 2.3 and 13.4 ± 7.5, respectively, $p<0.001$). Finally, participants with insomnia had a higher mean sleep environment score (53.7 ± 13.7) compared to those without insomnia (47.8 ± 14.3, $p=0.001$).

2. **Hierarchical Regression for Correlates of Insomnia**

   TABLE II shows the results of hierarchical regression analysis for correlates of insomnia. The analysis shows that at step one, the person dimension contributed significantly to the regression model, $F (3,170) = 7.91$, $p< 0.001$) and accounted for 12.2\% of the variation in insomnia. Introducing the variables under health/status dimension explained an additional
32.1% of variation in insomnia and this change in $R^2$ was significant, $F(4,166) = 23.96$, $p < 0.001$. Finally, adding the environmental dimension to the regression model explained an additional 2.5 % of the variation in insomnia and this change in $R^2$ was significant, $F(2, 164) = 3.823$ $p < 0.05$.

When all nine independent variables were included in step three of the regression model, ART adherence ($B= -0.736, SE=0.312, p=0.019$), anxiety ($B=0.284, SE=0.106, p=0.008$), pain ($B=0.308, SE=0.129, p=0.018$), fatigue ($B=0.178, SE=0.050, p=0.000$), and Islamic practice ($B= -0.124, SE=0.048, p=0.010$) were significant correlates of insomnia. The most important correlates of insomnia were variables under the health/status dimension (anxiety, fatigue, and pain) that uniquely explained 32.1% of the variation in insomnia. Together, the nine independent variables accounted for 46.8 % of the variance in insomnia.

3. Multivariate Logistic Regression for Correlates of Insomnia

TABLE III. shows unadjusted and adjusted associations with clinically-significant insomnia. After adjusting for gender and opioid use, clinically-significant insomnia was positively associated with anxiety (AOR = 1.15, 95% CI = 1.01-1.29, $p = 0.03$), pain (AOR = 1.17, 95% CI = 1.02-1.36, $p = 0.03$), fatigue (AOR = 1.09, 95% CI = 1.03-1.16, $p = 0.00$), and negatively associated with ART adherence (AOR = 0.62, 95% CI = 0.42-0.90, $p=0.01$).

E. Discussion

This study represents one of the first studies of insomnia in persons living with HIV (PLH) conducted in a low- or middle-income country. In this sample of HIV-infected and mostly drug-dependent adults receiving ART, one-third (33.5%) had ISI scores indicating insomnia, which by itself impacts daytime functioning and quality of life and may contribute to suboptimal ART adherence in this population. The rate of insomnia in this sample was higher compared to that of PLH in high-income countries (10-26%). [102] [24]. In order to investigate these aspects further, the demographic and clinical characteristics associations with clinically significant insomnia were analyzed also. No association was found between insomnia and demographic
data. This is contrary to what one of the most recent studies [8] found that having a partner was associated with better sleep. It was also noted that when absent of insomnia and clinically significant insomnia groups were compared, insomnia significantly differed by level of ART adherence, drug use, opioid use, anxiety, depression, pain, fatigue, sleep environment, and religious practice. These findings have also been documented in studies outside Indonesia [24]. HIV infection potentially predisposes or precipitates insomnia due to psychosocial stress associated with it. It is also possible that HIV infection triggers and prolongs insomnia through pathological process of neural injury [102].

Using hierarchical regression analysis, guided by Symptom Management Theory and placing insomnia under the symptom experience dimension, it was revealed that insomnia was associated with variables under the dimensions of person, health/illness, and environment. In comparison with the two other SMT dimensions; person and environment; variables under the health/illness dimensions (anxiety, pain, and fatigue) were the most significant correlates of insomnia. Collectively, ART adherence, anxiety, pain, fatigue, and religious practice were consistently found to be the correlates of insomnia. The association of insomnia with variables related to psychosocial and physiological morbidities identified in our study was in agreement with the results of other studies. In the general population, sleep is strongly associated with psychological parameters, including anxiety [50]. Through the mechanism that anxiety intensifies cortical and peripheral arousals, and increased arousal disturbs sleep initiation or maintenance, individuals with anxiety disorders have delayed sleep onset and reduced total sleep time [103]. Physiological morbidities, i.e. pain and fatigue, were also correlates of insomnia in our study. Pain and fatigue are the symptoms experienced by HIV infected individuals [8]. The risk of opportunistic infections that increased with HIV infection progression in this population produce various symptoms including pain and fatigue that can cause problems in falling asleep and may diminish sleep efficiency. Also, pain may cause non-restorative sleep in HIV positive individuals [89]. HIV infection activates several pro-
inflammatory cytokines, particularly interleukin 1 (IL-1), IL-6, and tumor necrosis factor a (TNF-a), each of which has roles in sleep, anxiety, pain and fatigue [56].

Our study found that among Muslim participants, practicing religion was associated with less insomnia. A previous study by Paine et al found similar results that those who had a strong belief in God, or felt they had real purpose in their life, experienced a better sleep compared to those who did not have strong beliefs. Those who regularly attended mosque or other places of worship were also more likely to demonstrate better sleep compared to those who did not [104]. An earlier study by Hayward et al has also connected spirituality to lower levels of anxiety and depression [105]. Furthermore, religious places such as mosques are often seen as a source of relaxation. The sense of community and support that's often associated with religious gatherings can help reduce stress, anxiety, and worry, which are known to affect sleep [106].

Another major finding to emerge from the current study was a significant association between insomnia and ART adherence, which persisted even after controlling for other demographics, HIV- and health-related variables, that was consistent with previous study [38]. A fundamental unresolved question that emerges from this study is whether poor adherence leads to insomnia through viremia that stimulates pro-inflammatory cytokines that affects cerebral functioning and sleep [102] or whether poor sleep is a cause of non-adherence by interfering with sleep schedule and daytime activities [24].

We also found that insomnia was associated with opioid use, as the side effects of addiction or withdrawal [107]. The majority of our study participants were in a methadone maintenance program. A previous study by Hsu et al reported insomnia in persons with opioid use disorders in a methadone detoxification program [30]. Conroy et al found that insomnia is a common complaint for all types of substance users; those who become dependent on either narcotics or stimulants. Those who use depressants such as alcohol to get to sleep may struggle when the substance is not available. Those who quit using substances often have to
deal with withdrawal symptoms that include a period of insomnia. Those who abuse stimulants commonly suffer from long periods of nonrestorative sleep [24]. Substance use affects neurotransmitter systems that regulate the sleep-wake system [24]. Many of the same neurotransmitter systems affected by substance use are involved in the regulation of sleep-wake systems. As a result, insomnia and sleep dysregulation may result at various stages of substance use or withdrawal [28].

F. Limitations and Strengths
Our study had several potential limitations. Although we employed standardized measures, one of them showed low Cronbach’s alphas, HADS-D for measuring depression. We speculate that the demonstrated low reliability of HADS in our context, may explain the finding that depression was not a correlate of poor sleep. To our understanding there was a limited tool for measuring sleep environment. We used a sleep environment index that has not been tested for its validity elsewhere. This measure however was developed specifically to our study and showed an excellent internal consistency. Another limitation is the use of convenience sampling, which could result in less generalizable findings. However, it can be generalized for the Indonesian HIV population, specifically in urban areas. We examined insomnia based on the questionnaire rather than objective measures; however, we used standardized instruments that were comparable to those used in other studies, and some experts suggest that self-reported data may be more representative of sleep issues. The cross-sectional design did not allow for assessing the causality between insomnia and its correlates.

The study had major strengths. We employed standardized and Indonesian-validated measures. Therefore, the study findings provided thorough and clear findings about the characteristics of insomnia and its correlates in adults living with HIV in Indonesia, especially in an urban area. This study involved samples that were substantially large and diverse of HIV positive people. We isolated the correlates of poor sleep in HIV in a context that has not been
explored intensively. These data contribute significantly to providing an important clue to the etiology of these sleep problems. This is valuable information for establishing the significance of insomnia among adults living with HIV. The use of standardized measures and clear documentation of the research process regarding the content and application of the instruments make it possible for other researchers to replicate the study in different areas, or over time, with the production of comparable findings. Clinically, our study findings provide evidence about the importance of screening for insomnia during HIV care.

Funding: This study was funded by the UIC AIDS International Training and Research Program, Grant Number D43 TW001419
TABLE I. Bivariate demographic and clinical association with insomnia in HIV-infected adults receiving ART in Jakarta, Indonesia (N=200)

<table>
<thead>
<tr>
<th>SMT Dimension/variable</th>
<th>Total Sample (%) (N=200)</th>
<th>Absent of insomnia (n=133)</th>
<th>Clinically significant insomnia (n=67)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Person domain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>43 (21.5)</td>
<td>31 (23.3)</td>
<td>12 (17.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age in years, (SD)</td>
<td>34.9 ± 5.0</td>
<td>35.2 ± 5.1</td>
<td>34.3 ± 4.7</td>
<td>NS</td>
</tr>
<tr>
<td>Completed high school</td>
<td>139 (69.5)</td>
<td>95 (71.4)</td>
<td>44 (65.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Married/in a relationship</td>
<td>119 (59.5)</td>
<td>79 (59.4)</td>
<td>40 (59.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Employed</td>
<td>127 (63.5)</td>
<td>87 (65.4)</td>
<td>40 (59.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Muslim religion</td>
<td>172 (86.0)</td>
<td>116 (87.2)</td>
<td>56 (83.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Ethnicity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Betawi</em></td>
<td>84 (42.0)</td>
<td>57 (42.9)</td>
<td>27 (40.3)</td>
<td>NS</td>
</tr>
<tr>
<td><em>Javanese</em></td>
<td>41 (20.5)</td>
<td>26 (19.5)</td>
<td>15 (22.4)</td>
<td></td>
</tr>
<tr>
<td><em>Sundanese</em></td>
<td>21 (10.5)</td>
<td>12 (9.0)</td>
<td>9 (13.4)</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>54 (27.0)</td>
<td>38 (28.6)</td>
<td>16 (23.9)</td>
<td></td>
</tr>
<tr>
<td>Mean months receiving ART (SD)</td>
<td>56.3 ± 42.0</td>
<td>57.5 ± 36.9</td>
<td>53.8 ± 50.9</td>
<td>NS</td>
</tr>
<tr>
<td>Mean ART adherence (SD)</td>
<td>4.4 ± 1.0</td>
<td>4.5 ± 1.0</td>
<td>3.9 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drug use within previous 1 year:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any drugs or alcohol</td>
<td>109 (54.5)</td>
<td>63 (47.4)</td>
<td>46 (68.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Any opioids</td>
<td>46 (23.0)</td>
<td>21 (15.8)</td>
<td>25 (37.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Currently receiving methadone</td>
<td>111 (55.5)</td>
<td>72 (54.1)</td>
<td>39 (58.2)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Health/illness domain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety score, mean ± SD</td>
<td>6.0 ± 3.8</td>
<td>4.8 ± 3.4</td>
<td>8.4 ± 3.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depression score, mean ± SD</td>
<td>6.3 ± 3.2</td>
<td>5.5 ± 3.1</td>
<td>7.9 ± 2.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pain, mean score ± SD</td>
<td>2.6 ± 2.7</td>
<td>1.8 ± 2.3</td>
<td>4.1 ± 2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatigue, mean score ± SD</td>
<td>16.5 ± 9.0</td>
<td>13.4 ± 7.5</td>
<td>22.9 ± 8.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Environmental domain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean sleep environment score (SD)</td>
<td>49.8 ± 14.4</td>
<td>47.8 ± 14.3</td>
<td>53.7 ± 13.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean Islamic practice score (SD)</td>
<td>45.1 ± 8.16</td>
<td>46.9 ± 7.68</td>
<td>41.3 ± 7.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Legend: SMT=Symptom Management Theory; ART=antiretroviral therapy; NS=Not significant at p<0.05
### TABLE II. Summary of hierarchical regression for correlates of insomnia (N=172)

<table>
<thead>
<tr>
<th>SMT Domain/variable</th>
<th>Model I B</th>
<th>SE B</th>
<th>Beta</th>
<th>Model II B</th>
<th>SE B</th>
<th>Beta</th>
<th>Model III B</th>
<th>SE B</th>
<th>Beta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>-0.082</td>
<td>0.962</td>
<td>-0.006</td>
<td>0.694</td>
<td>0.808</td>
<td>0.052</td>
<td>1.111</td>
<td>0.81</td>
<td>0.083</td>
</tr>
<tr>
<td>Opioid use</td>
<td>3.330</td>
<td>1.008</td>
<td>0.241**</td>
<td>1.332</td>
<td>0.843</td>
<td>0.096</td>
<td>1.127</td>
<td>0.835</td>
<td>0.081</td>
</tr>
<tr>
<td>ART adherence</td>
<td>-1.174</td>
<td>0.386</td>
<td>-0.221**</td>
<td>-0.772</td>
<td>0.317</td>
<td>-0.145*</td>
<td>-0.736</td>
<td>0.312</td>
<td>-0.139*</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.336</td>
<td>0.106</td>
<td>0.222**</td>
<td>0.284</td>
<td>0.106</td>
<td>0.188**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>0.115</td>
<td>0.130</td>
<td>0.063**</td>
<td>0.015</td>
<td>0.133</td>
<td>0.008</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>0.351</td>
<td>0.130</td>
<td>0.178**</td>
<td>0.308</td>
<td>0.129</td>
<td>0.156*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.193</td>
<td>0.050</td>
<td>0.309**</td>
<td>0.178</td>
<td>0.050</td>
<td>0.285**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep environment</td>
<td>0.032</td>
<td>0.023</td>
<td>0.081</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Islamic practice</td>
<td></td>
<td></td>
<td>-0.124</td>
<td>0.048</td>
<td>0.180*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* R² = 0.122
** R² change = 0.122
* F for change in R² = 7.909**
** F for change in R² = 23.96**
* Correlation is significant at the 0.05 level
** Correlation is significant at the 0.01 level

### TABLE III. Independent and multivariate logistic regression for correlates of insomnia (N=200)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR</th>
<th>p-value</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>0.718</td>
<td>0.382</td>
<td>0.34-1.51</td>
<td>1.031</td>
<td>0.949</td>
<td>0.40-2.67</td>
</tr>
<tr>
<td>Opioid use</td>
<td>3.175</td>
<td>0.001*</td>
<td>1.61-6.27</td>
<td>2.072</td>
<td>0.123</td>
<td>0.82-5.22</td>
</tr>
<tr>
<td>ART adherence</td>
<td>0.565</td>
<td>0.000*</td>
<td>0.41-0.77</td>
<td>0.604</td>
<td>0.008*</td>
<td>0.42-0.88</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.337</td>
<td>0.000*</td>
<td>1.21-1.48</td>
<td>1.144</td>
<td>0.029*</td>
<td>1.01-1.29</td>
</tr>
<tr>
<td>Depression</td>
<td>1.300</td>
<td>0.000*</td>
<td>1.17-1.45</td>
<td>1.104</td>
<td>0.189</td>
<td>0.95-1.28</td>
</tr>
<tr>
<td>Pain</td>
<td>1.373</td>
<td>0.000*</td>
<td>1.22-1.55</td>
<td>1.167</td>
<td>0.036*</td>
<td>1.01-1.35</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.159</td>
<td>0.000*</td>
<td>1.11-1.22</td>
<td>1.088</td>
<td>0.004*</td>
<td>1.03-1.15</td>
</tr>
<tr>
<td>Sleep environment</td>
<td>1.029</td>
<td>0.007*</td>
<td>1.01-1.05</td>
<td>1.009</td>
<td>0.519</td>
<td>0.98-1.04</td>
</tr>
</tbody>
</table>

Significant at the 0.05 level; OR=odds ratio; ART=antiretroviral therapy
Figure 1. Study framework for characteristic and correlates of insomnia in HIV

Figure 2. Insomnia in people living with HIV in Jakarta Indonesia
A. **Abstract**

**Background**: Prior research has widely recognized poor sleep, fatigue, and pain as important negative predictors of quality of life (QoL) among people with chronic diseases. To date, no studies have explored how these physical symptoms operate together and affect QoL in people living with HIV (PLH). The purpose of this study was to examine the relationships among self-reported sleep, fatigue, pain, and quality of life. **Methods**: PLH (N = 200) receiving antiretroviral therapy (ART) were recruited from an HIV community organization in Jakarta, Indonesia. Standardized scales for self-reported sleep, fatigue, pain, ART adherence, substance use, and QoL were used to measure key study variables. Descriptive statistics, bivariate correlation, and multivariate linear regression were conducted. **Results**: Using Pittsburgh Sleep Quality Index (PSQI) global score cut off point >5, almost two-thirds of the participants (67%) indicated poor sleep and using ISI total score cut off >10, about one-third (33.5%) of the participants indicated clinically significant insomnia. QoL was significantly negatively correlated with low sleep quality ($r = -0.377$, $p<0.01$), insomnia ($r = -0.512$, $p<0.01$), fatigue ($r = -0.634$, $p<0.01$), and pain ($r = -0.321$, $p<0.01$); but positively correlated with ART adherence ($r = 0.167$, $p<0.05$). Adjusting for gender, level of education, drug/alcohol use, and ART adherence, QoL was negatively associated with fatigue ($B = -0.762$, $SE = 0.113$, $p<0.001$), insomnia ($B = -0.519$, $SE = 0.176$, $p = 0.004$), and methadone treatment ($B = -4.208$, $SE = 1.762$, $p = 0.018$). The model uniquely explained 48% of the variance in QoL. **Conclusion**: The findings clarified the association between QoL with two important physical HIV symptoms (fatigue and insomnia) and being in methadone treatment while living on ART. This highlights the need for future interventions to target these physical symptoms and substance use to improve QoL among PLH on ART. **Keywords**: antiretroviral therapy, adherence, Indonesia, substance use, sleep, quality of life
B. Introduction

The global HIV pandemic continues to be a major public health issue, with more than 75 million people living with HIV (PLH) worldwide [108]. With the recent improvements in prophylactic and therapeutic regimens, HIV has been transformed into a chronic medical condition with near normal life expectancy [109], leading to an emerging focus on quality of life (QoL) [110]. The major goal of HIV care, in addition to viral suppression, is effective symptom management meant to eliminate or minimize the impact of disease in order to enhance optimal health state and QoL [65]. As with any other chronic illness, PLH face numerous physical comorbidities such as poor sleep, fatigue, and pain, that can affect their QoL [111]. The complex situation that includes HIV infection and its comorbidities has generated an urgency to maximize the QoL experienced by PLH [64].

QoL is a multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning [109]. QoL is a key outcome measure for treatment [65, 112, 113]. QoL is an important variable that can be a direct measure of population health, life expectancy, and causes of death [65]. QoL is used to measure the effects of chronic illness, treatments, and short- and long-term disabilities [114]. There is a large body of evidence that physical symptoms such as poor sleep are related to lower QoL [65, 71, 115, 116]. In general and in other chronic disease populations, including among the HIV population, the association between sleep and quality of life has been extensively studied and confirmed to exist [117]. A previous study by Phillips et al. examined the associations of sleep quality (measured using PSQI) and QoL measured using Short-Form Health Survey (SF-36) in 144 HIV-infected African-American women. They found that sleep quality was associated with QoL independent of the individual's stage of illness [66]. In addition to the poor sleep, previous studies confirmed that pain and fatigue are important symptoms that adversely affect QoL of people with chronic diseases [118-122]. Previous studies have also shown that people with chronic diseases experience fatigue, have greater sleep problems and also decreased QoL [123]. Similarly, lower
overall quality of life was associated with the presence of pain and poor sleep [124, 125]. Poor sleep, fatigue, and pain are among the top physical complaints by HIV infected persons that may impact QoL [64]. The relationship between pain, fatigue, poor sleep and QoL is important to explore in order to improve care of PLH [118].

Poor sleep is a common issue in substance-dependent individuals [27, 30, 126]. A study found that 70.2% of this population indicated poor sleep [30]. Difficulty falling asleep and staying asleep or poor quality sleep, symptoms associated with poor sleep and insomnia are frequent among opioid-dependent individuals. The side effects of addiction or withdrawal result in poor sleep [27]. Poor sleep was associated with as sedative medication abuse, alcohol abuse or heroin relapse [31]. In addition, substance use has also been found to be a significant predictor of lower QoL [127-130]. Poor sleep, substance use, and QoL are strongly linked [131].

Previous studies have found that poor HIV medication adherence was associated with poor sleep [38, 132] and high HIV symptom severity. Medication adherence was associated with self-reported HIV symptom severity via the partial mediation role of poor sleep [38]. Controlling for other variables, HIV medication adherence has also been found to significantly predict QoL [127]. Consistent adherence is associated with better outcomes including improved QoL [133].

Although prior research has widely recognized fatigue, pain, and poor sleep as important correlates of QoL, to date, research has typically focused on the individual physical symptoms on QoL of PLH. Furthermore, little is known about the association of substance use and ART adherence with QoL altogether in a model with those physical symptoms among PLH. The possible ways and the extent to which a similar association can occur when these variables were put together, particularly among PLH, remains an important unanswered question. A better understanding of how those variables influence QoL is critical in developing future programs designed to improve QoL among this key population. To date, no studies have examined the relationships between self-reported sleep, other symptoms and quality of life in PLH. Therefore,
The purpose of this study is to examine relationships among self-reported sleep, fatigue, pain, substance use, ART adherence, and quality of life in PLH.

Theoretically-based research that examines HIV physical symptoms together with drug/alcohol use and ART adherence as correlates of QoL in PLH is required to inform more efficacious interventions. The present study is guided by the University of California San Francisco Symptom Management Theory (UCSF SMT), depicted in Figure 1. The SMT is a middle-range theory that includes 3 components of symptom management: the symptom experience, symptom management strategies, and outcomes; and 3 dimensions of person, health/illness, and environment [134]. This theory allows for QoL as an outcome to be understood within the context of various health concerns that fit into the domains of person (gender, substance use, ART adherence), health/illness (fatigue, pain), and symptom experience (self-reported sleep).

C. Methods

1. Research Design

This study used cross-sectional design to collect quantitative data about self-reported sleep, associated symptoms, and quality of life. The study design was appropriate to capture the sleep nature with a one-time measurement, while at the same time determining the associations between independent and dependent variables [135]. Convenience sampling technique was used to approach potential participants.

Over a four month period (May to September 2016), a number of 200 PLH were recruited to complete paper-based surveys measuring self-reported sleep, fatigue, pain, substance use, adherence to ART, and QoL. Ethical approvals were obtained from two institutional review boards (IRBs) at the University of Illinois at Chicago and Universitas Indonesia. Approval was also granted by the study setting. All participants provided written informed consent prior to study enrollment.
2. **Study Setting and Participants**
This study was conducted at KIOS Atma Jaya, a community organization that was established in 2002, as a response to the increase of HIV prevalence among injecting drug users in Jakarta. The center provides the following services: harm reduction for injecting drug users, case management, referral to methadone treatment, sexually transmitted infection testing including HIV, and primary health care. To date 5000 injecting drug users have utilized KIOS services.

Eligible participants were 18 years or older, HIV-infected by self-report, receiving ART for at least 3 months (confirmed by drug prescription card), and provided informed consent. Potential participants with a Karnofsky performance score ≤ 40% (severely disabled or likely to be admitted to the hospital) were excluded [8].

3. **Sample Size Estimates**
Sample size was determined based on power analysis for linear multiple regression: fixed model R2 increase using G*Power software version 3.1.9.2. In this study, the total number of tested correlates was eight; gender, level of education, drug/alcohol use, methadone treatment, ART adherence, self-reported sleep, fatigue, and pain. Using alpha level of 0.05, effect size of 0.05, and power of 0.85 (recommended power above 0.80), the minimum sample size required is 146. However, the sample was increased to 200 in anticipation of missing data. Considering the feasibility of conducting the study, the sample size of 200 was the ideal achievable number. The effect size ($f^2=0.05$) was comparable to an $R^2$ increase of 5% for an individual variable and was considered useful in detecting small (or larger) correlates of sleep quality. In comparison, a previous study indicated both fatigue and pain explained by 0.34 of variance in sleep quality among HIV individuals [74].

4. **Survey Measures**
The quantitative data that was collected includes: self-reported sleep, substance use, ART adherence, anxiety, depression, fatigue, pain, sleep environment, religious practice, and
quality of life; clinical data; and demographic information. Official permission was sought from the instrument developers. As the participants were non-English speakers, we used translated and validated instruments in the Indonesian context. All data were collected using questionnaires.

**Quality of life** was assessed using a measure developed by the World Health Organization, WHOQOL-HIV BREF. The WHOQOL-HIV has 31 items and covers 6 domains: Physical, Psychological, Level of Independence, Social Relationships, Environment, and Spirituality. Each item is based upon a self-report using a 5-point scale. Respondents then were asked to check one of the following degrees: 'not at all,' 'a little,' 'moderately,' 'mostly,' and 'completely.' Possible scores range from 31-155. Higher total score indicates higher quality of life, with a score <60 indicating “unsatisfied QoL” [136]. The WHOQOL HIV BREF has been found to be valid and reliable in different contexts [137]. The WHOQOL BREF has been used in several studies in Indonesia [138] [91]. Its Cronbach’s alpha in this study was α =0.92.

**Self-reported sleep** was measured using the Pittsburgh Sleep Quality Index (PSQI) and the Insomnia Severity Index (ISI) [87]. The PSQI consists of 19 items measuring seven components; sleep efficiency, sleep duration, sleep latency, sleep disturbance, daytime dysfunction, sleep quality overall, and use of sleep medication during the previous month. Composite scores calculated from subscales range from 0 to 21, with scores > 5 indicating *poor sleep*. The seven individual components’ composite scores were calculated using formulas recommended by the PSQI developer with minimum score = 0 (better) and maximum score = 3 (worse) [139]. During the PSQI development, acceptable measures of internal homogeneity, consistency (test-retest reliability), and validity were obtained [139]. Reliability of the PSQI Indonesia was obtained from the developer. The Cronbach’s alpha in our study was acceptable (0.68). The term *insomnia* was used to describe poor self-reported sleep measured using the Insomnia Severity Index (ISI>10). The ISI measures insomnia
severity, a construct related to but more specific than sleep quality [87]. The ISI was designed to assess the nature, severity, and impact of insomnia in adults. It consists of seven items that ask about severity of sleep onset, sleep maintenance and early morning wakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties[88]. Scaling of the items is done using the 5 point Likert scale (0=no problem, 4=very severe problem). Reliability tests done by the ISI developer included test-retest and internal consistency (Cronbach’s α = 0.91) [89]. Procedures to achieve validity done by the ISI developer included face and content validity; the ISI has been found to be correlated with sleep diaries, polysomnography, and interviews[87]. In an Indonesian study, ISI has been found to be a reliable measure with Cronbach’s alpha internal consistency 0.99 [140]. Possible total scores range from 0 to 28, with total score >10 indicating clinically significant insomnia [87]. ISI mean scores were also categorized as “absent” (≤7); “sub-threshold” (8-14); “moderate” (15-21), or “severe insomnia” (22-28) [90]. Cronbach’s alpha for the ISI in our study was high (α=0.88).

**Fatigue** was measured using the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue Scale), a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function. The FACIT-Fatigue Scale uses a 5-point Likert-type scale from 0 “Not at all” to 4 “Very Much”. Two items were reverse scored. Possible scores range from 0-52, with a score >30 indicating “severe fatigue” [98]. Subsequent to its development, it has been employed in over 150 published studies including over 40,000 people from different chronic illness including HIV/AIDS. In all cases, the FACIT-Fatigue Scale has been found to be reliable and valid [99]. Cronbach’s alpha for FACIT-Fatigue Scale in this study was high (α=0.90).

**Pain** was assessed using the Numeric Pain Rating Scale (NPRS), which measures the pain severity and is often used to evaluate treatment response. Participants were asked to rate their pain in the last seven days, on a numeric scale from “0” no pain at all to “10” worst pain
imaginable. High test–retest reliability has been observed in both literate and illiterate patients \((r = 0.96\) and \(0.95,\) respectively) [97].

**HIV Treatment factors** included year of HIV diagnosis and months receiving ART. ART adherence was measured with the single–item self-rating scale (SRSI) that uses qualitative adjectives arranged in a 5-point Likert-type scale, from “very poor” to “excellent” to describe medication adherence during the last 30 days. This single item measure is easy to administer in a clinical setting, not prone to ceiling effects, and as good as or better than other adherence measures at predicting adherence-related clinical outcomes such as HIV viral load and CD4+ cell count [92, 93].

**Drug and alcohol use** was assessed for the 30 days before study enrollment using the Texas Christian University (TCU) drug screen II, previously adapted for Indonesia [91]. The adapted version of the TCU II includes 15 items measuring type, route, and frequency of drug use, recurring consequences for drug use, and withdrawal symptoms. A single question was used to assess current methadone use.

**Demographics** collected included: age, gender, education, marital/relationship status, employment, and religion. Participants were also asked when they were diagnosed with HIV and when they were initiated on ART.

5. **Procedure**

   The Principle investigator (PI) and a research assistant (RA) were involved in data collection. In order to ensure uniformity, the RA was recruited based on set criteria and was trained to make sure that the RA asked the questions in a similar manner to the PI. The PI and RA collected data using interviewer administered questionnaires.

   Recruitment was conducted in the following steps: 1) flyers were provided and displayed at the KIOS where the study was conducted that contained the researchers’ phone number; 2) interested potential participants called the researcher or talked to the officer of the organization; 3) a date and time for meeting the potential subjects was set when they
contacted the researcher; 4) upon meeting the potential subjects, the researcher screened the potential participants using the Karnofsky Scale; 4) the researcher provided free and informed consent; and 5) the researcher interviewed the participants. Participants were compensated for their time and transport costs amounting to a total of $10.

6. **Statistical Analysis**
   Data were analyzed using the IBM SPSS Statistics version 23. All continuous variables were checked for normality of distribution by looking at kurtosis and skewness, visual inspection of histograms, and Q–Q plots. No outliers were found. There were no missing data and no variables were required to be transformed. Descriptive statistics, means and standard deviations for continuous, and percentages for categorical variables were calculated for all measures, including demographic characteristics.

   To identify associations among key variables, bivariate correlations and linear regression were conducted using Enter method. Variable selection was based on the SMT, empirical data, and the statistical significance in bivariate analysis. Prior to conducting multiple regression, the relevant assumptions of this statistical analysis were tested. A sample size of 200 was adequate given eight independent variables to be included in the analysis. The assumption of singularity was also met as the independent variables were not a combination of various independent variables. An examination of collinearity revealed that no independent variables were highly correlated (r>0.7). The collinearity statistics (i.e., Tolerance and VIF) were all within acceptable limits; the assumption of multicollinearity was considered to have been met [101].

   The WHOQOL-HIV BREF total score was the dependent variable. Gender, level of education, drug/alcohol use, methadone treatment, self-reported sleep (ISI total score), fatigue, and pain were the independent variables. Significance was set at p< 0.01 and < 0.05 for all analyses.
D. Results

1. Demographic and Clinical Characteristics of Study Participants

A total of 200 adults living with HIV participated in this study. TABLE IV. shows that participants were predominantly male (78.5%) and Muslim (86.0 %). On average, the participants were in their thirties (mean age of 34.9 ± 5.0); had been diagnosed with HIV as well as initiated ART for about five years at the time of the study (mean score 6.90 ± 4.1 and 4.72 ± 4.0 respectively); and adhered to ART at the levels of “good” and “very good” (mean score 4.4 ± 1.0). More than a half of the total participants completed high school (69.5%), were married/in a relationship (59.5%), employed (63.5%), using drug or alcohol in the past 12 months (54%) and under methadone treatment (55.5%).

Using PSQI global score cut off point >5, almost two-thirds of the participants (67%) indicated poor sleep and using ISI total score cut off >10, about one-third of the participants (33.5%) indicated clinically significant insomnia. Of the seven PSQI components, participants indicated more problems on sleep latency and sleep disturbance (mean score 1.65 ± 0.9 and 1.46 ± 0.6 respectively, 0=better 3=worse). In general, participants were in mild pain (mean score 2.6 ± 2.7), non-severe fatigue (mean score 16.5 ± 9.0, cut off ≤30), and satisfactory QoL (mean score of 105.70 ± 14.7, cut off ≥60).

When the demographics and clinical characteristics were compared between males and females, female participants were younger, had a shorter duration of HIV diagnosis, experienced less pain in the last 7 days, and had better QOL. A larger proportion of females were employed, not using drug/alcohol or on methadone treatment, and either married or in a relationship. These differences were all statistically significant (p<0.05).

2. Bivariate Correlations of Variables of Interest

TABLE V. presents bivariate correlations of variables of interest. QoL was significantly negatively correlated with low sleep quality (r=-0.377, p<0.01), insomnia (r= -0.512, p<0.01),
fatigue ($r = -0.634, p<0.01$), and pain ($r = -0.321, p<0.01$); but positively correlated with ART adherence ($r = 0.167, p<0.05$).

3. **Multivariate Linear Regression of Association of Variables of Interest**

   TABLE VI. shows multivariate associations of the key variables. After adjusting for gender, level of education, drug/alcohol use, and ART adherence, QoL was negatively associated with fatigue ($B = -0.762, \ SE = 0.113, p<0.001$), insomnia ($B = -0.519, \ SE = 0.176, p=0.004$), and methadone treatment ($B = -4.208, \ SE = 1.762, p=0.018$). The model uniquely explained 48% of the variance in QoL.

E. **Discussion**

   The present study dealt with the association between self-reported sleep, fatigue, pain, substance use, ART adherence, and QoL in a population of adults living with HIV that are on ART. We involved 200 participants, with 54.5% who used drug/alcohol in the last 12 months and 55.5% on methadone treatment. The key finding of this study was that, adjusted for gender, level of education, drug/alcohol use, and ART adherence, QoL was negatively associated with fatigue, self-reported sleep (insomnia), and methadone treatment.

   In our study one-third (33.5%) of the participants indicated clinically significant insomnia according to ISI and almost two-thirds (67%) of them indicated poor sleep according to PSQI. The high percentage of poor sleep in our study participants is expected. A most recent meta-analysis identified that poor sleep among the HIV population ranged from 29 to 97% with a global estimate of 58.0%. Previous studies have associated insomnia in HIV with neurobiological defects and immune system modulation as potential mechanisms to explain that high percentage [14]. HIV infection was significantly associated with alterations of intracellular pro-inflammatory cytokines i.e. Tumor Necrosis Factor-α, Interferon-γ, and Interleukin-12 that are involved in sleep regulation [77, 141].

   Insomnia in our study population is an independent associate of QoL. This is in agreement with previous findings in other patient populations [119, 123, 131, 142]. Our
findings depict insomnia as undermining quality of life in adults living with HIV. We found that of the seven components of PSQI, participants experienced problems mainly in sleep latency, sleep disturbance, daytime functioning, and overall sleep quality. The extended sleep latency may also be related to substance use. A previous study found that decreased sleep time, increased sleep latency and wake time after sleep onset, and deficiency were typical among substance abusers [28, 33]. A previous study found that higher levels of wakefulness after sleep onset were also indirectly related to lower levels of quality of life [115]. Other previous studies found that HIV infected persons had more prevalence of daytime sleepiness that reduced QoL [71]. Studies on sleep patterns in insomnia populations have repeatedly pointed to the importance of regular sleep times and sleep duration. Individuals with insomnia are reported to have more variable sleep times than healthy people, and it has been suggested that day-to-day variability in sleep times/sleep duration may be a mechanism that sustains symptoms of insomnia [115]. Individuals who sleep poorly on one night may experience feelings of fatigue and sleepiness [143], resulting in worse sleep the following night, and eventually compromise quality of life [71].

In our study, fatigue was found to be an important construct in explaining how patients perceive their quality of life. Previous studies have identified fatigue as a common and distressing symptom among people living with HIV [144-146], even among those who are optimally treated [103]. Fatigue is a disabling symptom in which physical and cognitive function is limited by interactions between performance fatigability and perceived fatigability [147]. In our study we measured fatigue using a self-reported method. Previous studies have found that HIV infection induces fatigue by the current hypothesized mechanism that inflammatory pathways may be involved in the production of fatigue [148]. Fatigue is a result of elevated levels of cytokines, particularly interleukin 10 (IL-10) [149] and (IL-6) [59, 150]. A previous study has also clarified how fatigue could have adverse impact on QoL. The study suggests that fatigue interferes with important aspects of human life, including the cognitive ability,
performance of household tasks, physical exercise, and work, leading to poor quality of life. Fatigue might also have economic implications when it hinders people’s ability to function optimally at work, maintain a household, or fail to work altogether. HIV-related fatigue could be a burden for employment due to decreased motivation, reduced concentrating, and tiredness [146]. A study found that individuals with a higher income experienced less fatigue. This may be because they are able to hire others or the type of their jobs that are less physically demanding. It may also explain the fact that less fatigued individuals can work more hours and therefore get higher salaries [151].

An unexpected finding of our study was that being on methadone treatment negatively contributes to quality of life. Intuitively, being on treatment was expected to improve the patients’ quality of life. It is speculated that this seemingly contradictory finding could be indicative of the fact that those on treatment are patients struggling with drug abuse problems, leading to low quality of life. It is therefore important that future studies should explore the relationship between methadone use and quality of life in the Indonesian context using longitudinal approaches that include control groups.

Insomnia and fatigue could impact daily living activities that are essential for disease management, including medication adherence and ultimately overall patient quality of life. It is therefore important that HIV management should include addressing the impacts of fatigue, insomnia and drug abuse in order to improve patients’ quality of life.

Our study has limitations. Although we employed standardized measures, one of them (PSQI) showed Cronbach’s alphas, in the level of acceptable. In multivariate analysis we used ISI data that were collected from a measure that had an excellent Cronbach’s alpha. The results from the self-reported measure of assessing sleep may be compromised given that subjects could provide socially desirable responses. The use of convenience sampling could result in less generalizable findings. With cross-sectional data, we cannot establish the sequence of events or determine causality.
This study, however, is the first to examine the relationship of self-reported sleep, fatigue, pain, ART adherence, and substance use on QoL in PLH, particularly in the study context. Our study resulted in evidence that living with HIV with its physical symptoms i.e. fatigue and pain as well as being in methadone treatment could significantly diminish QoL. Secondly, by employing a standardized, contextually valid method of measuring sleep, the study’s findings provide a thorough and clear picture of sleep in adults living with HIV in an urban area in Indonesia. A clear documentation of the research process regarding the content and application of the instruments makes it possible for other researchers to replicate the study easily in different areas, or over time, with the production of comparable findings.

Funding: The study was funded by UIC AIDS International Training and Research Program, Grant Number D43 TW001419
<table>
<thead>
<tr>
<th>SMT Dimension/variable</th>
<th>Total Sample (N=200)</th>
<th>Male (n=157)</th>
<th>Female (n=43)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Person</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years, mean ± SD</td>
<td>34.9 ± 5.0</td>
<td>35.5 ± 5.1</td>
<td>32.9 ± 3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Completed high school</td>
<td>139 (69.5)</td>
<td>108 (68.8)</td>
<td>31 (71.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Married/in a relationship</td>
<td>119 (59.5)</td>
<td>83 (52.9)</td>
<td>36 (87.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Employed</td>
<td>127 (63.5)</td>
<td>51 (32.5)</td>
<td>22 (51.2)</td>
<td>0.024</td>
</tr>
<tr>
<td>Muslim religion</td>
<td>172 (86.0)</td>
<td>132 (84.1)</td>
<td>40 (93.0)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>HIV Treatment Factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year HIV diagnosis, mean ± SD</td>
<td>6.90 ± 4.1</td>
<td>7.22 ± 4.2</td>
<td>5.72 ± 3.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Year receiving ART, mean ± SD</td>
<td>4.72 ± 4.0</td>
<td>4.79 ± 3.1</td>
<td>4.48 ± 4.2</td>
<td>NS</td>
</tr>
<tr>
<td>Adherence to ART ± SD</td>
<td>4.4 ± 1.0</td>
<td>4.38 ± 1.0</td>
<td>4.23 ±1.0</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Drug use within previous 1 year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any drugs or alcohol</td>
<td>109 (54.5)</td>
<td>95 (60.5)</td>
<td>14 (32.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Current methadone therapy</td>
<td>111 (55.5)</td>
<td>101 (64.3)</td>
<td>10 (23.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Health/illness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep quality (PSQI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global score, mean ± SD</td>
<td>7.61 ± 3.7</td>
<td>7.67 ± 3.8</td>
<td>7.40 ± 3.1</td>
<td>NS</td>
</tr>
<tr>
<td>Poor sleep (PSQI global score &gt;5)</td>
<td>134 (67.0)</td>
<td>106 (67.5)</td>
<td>28 (65.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Sleep efficiency, mean ± SD</td>
<td>0.62 ± 1.0</td>
<td>0.62 ± 1.0</td>
<td>0.63 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Sleep duration, mean ± SD</td>
<td>0.63 ± 1.0</td>
<td>0.65 ± 1.0</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>SMT</td>
<td>ART</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>Sleep latency, mean ± SD</td>
<td>1.65 ± 0.9</td>
<td>1.62 ± 0.9</td>
<td>1.79 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Sleep disturbance, mean ± SD</td>
<td>1.46 ± 0.6</td>
<td>1.45 ± 0.6</td>
<td>1.49 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Daytime functioning, mean ± SD</td>
<td>1.28 ± 0.9</td>
<td>1.30 ± 0.9</td>
<td>1.23 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Sleep quality overall, mean ± SD</td>
<td>1.24 ± 0.9</td>
<td>1.27 ± 0.9</td>
<td>1.16 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Sleep medication, mean ± SD</td>
<td>0.74 ± 1.1</td>
<td>0.79 ± 1.1</td>
<td>0.56 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Insomnia (ISI) total score, mean ± SD</td>
<td>8.65 ± 5.8</td>
<td>8.78 ± 6.1</td>
<td>8.16 ± 4.8</td>
<td>NS</td>
</tr>
<tr>
<td>Clinically significant insomnia (ISI&gt;10)</td>
<td>67 (33.5%)</td>
<td>55 (35.5%)</td>
<td>12 (27.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Pain score, mean ± SD</td>
<td>2.6 ± 2.7</td>
<td>2.8 ± 2.9</td>
<td>1.81 ± 2.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Fatigue total score, mean ± SD</td>
<td>16.5 ± 9.0</td>
<td>17.05 ± 9.0</td>
<td>14.91 ± 8.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Outcome**

<table>
<thead>
<tr>
<th>Quality of life total score, mean ± SD</th>
<th>SMT</th>
<th>ART</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>105.70 ± 14.7</td>
<td>104.48 ± 14.0</td>
<td>110.14 ± 16.2</td>
</tr>
</tbody>
</table>

Legend: SMT=Symptom Management Theory; ART=antiretroviral therapy; NS=Not significant at p<0.05
TABLE V. Correlations among study variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Quality of life</th>
<th>Sleep quality</th>
<th>Insomnia</th>
<th>Fatigue</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of life</td>
<td>1</td>
<td>-0.377**</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep quality (PSQI)</td>
<td>-0.512**</td>
<td>0.704**</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia (ISI)</td>
<td>-0.634**</td>
<td>0.450**</td>
<td>0.577**</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>-0.321**</td>
<td>0.347**</td>
<td>0.413**</td>
<td>0.399**</td>
<td>1</td>
</tr>
<tr>
<td>Pain</td>
<td>0.167*</td>
<td>-0.243**</td>
<td>-0.243**</td>
<td>-0.109</td>
<td>-0.199**</td>
</tr>
</tbody>
</table>

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

TABLE VI Multivariate linear regression with quality of life (N=200, R²= 0.48)

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>Beta</th>
<th>t</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Constant)</td>
<td>117.90</td>
<td>6.855</td>
<td>1</td>
<td>0.0</td>
<td>10</td>
<td>131.4</td>
</tr>
<tr>
<td>Female</td>
<td>1.753</td>
<td>2.092</td>
<td>0.048</td>
<td>0.4</td>
<td>-</td>
<td>5.879</td>
</tr>
<tr>
<td>Completed high school</td>
<td>3.033</td>
<td>1.792</td>
<td>0.093</td>
<td>1</td>
<td>0.0</td>
<td>6.568</td>
</tr>
<tr>
<td>Pain</td>
<td>0.026</td>
<td>0.324</td>
<td>0.005</td>
<td>0.9</td>
<td>-</td>
<td>0.666</td>
</tr>
<tr>
<td>Fatigue</td>
<td>-0.762</td>
<td>0.113</td>
<td>-0.456</td>
<td>0.0</td>
<td>-</td>
<td>-0.54</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>------------------------------</td>
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<td>---</td>
</tr>
<tr>
<td>Insomnia</td>
<td>-0.519</td>
<td>0.176</td>
<td>-0.201</td>
<td>-</td>
<td>0.0</td>
<td>-</td>
</tr>
<tr>
<td>Drug/alcohol use</td>
<td>-1.339</td>
<td>1.694</td>
<td>-0.044</td>
<td>-</td>
<td>0.4</td>
<td>-</td>
</tr>
<tr>
<td>ART adherence</td>
<td>1.245</td>
<td>0.803</td>
<td>0.086</td>
<td>1</td>
<td>0.1</td>
<td>-</td>
</tr>
<tr>
<td>Methadone treatment</td>
<td>-4.208</td>
<td>1.762</td>
<td>-0.139</td>
<td>-</td>
<td>0.0</td>
<td>-</td>
</tr>
</tbody>
</table>

**Correlation is significant at the 0.01 level (2-tailed).**

*Correlation is significant at the 0.05 level (2-tailed).
CITED LITERATURE


140. Swanengyun, G., *Validity and reliability of Insomnia Severity Index-Indonesia on homeless teenagers in Yogyakarta, in Fakultas Kedokteran.* 2015, Gajahmada University.


VITA

Hening Pujasari
3700 S Hermitage Ave Apt 1R
Chicago, Illinois 60609
hpajas2@uic.edu

EDUCATION

Current  PhD Candidate. University of Illinois at Chicago College of Nursing, Chicago, Illinois, United States

2008  Master of Nursing. University of Melbourne, School of Nursing, Melbourne, Australia
Stream: Emergency nursing
Minor thesis: Nursing students ’and nurse educators’ perceptions and attitudes towards bioscience in an Indonesian Bachelor of Nursing program.

2006  Master of Biomedical Science. Universitas Indonesia Faculty of Medicine, Jakarta Indonesia
Major: Pathobiology
Thesis: In vitro effect of Red Fruit Oil (Pandanus Conoideus Lam.) on apoptosis activity and growth inhibition of C3H Mice Milk Glands Tumor Cells

1999  Bachelor of Nursing. Universitas Indonesia Faculty of Nursing, Depok Indonesia
Thesis: Stress and coping patterns among Indonesian Bachelor of Nursing Science students

AWARDS

The 2016-2017 College of Nursing PhD Student Research Award, University of Illinois College of Nursing.

The Beverly J. McElmurry Award 2016-2017, the University of Illinois College of Nursing

Fogarty UIC AIDS International Training and Research Program (doctoral trainee), John E. Fogarty International Center and the National Institute of Nursing Research at the National Institute of Health, 2013-current

Australian Development Scholarship (master degree scholarship), AusAID Australian Government, 2006-2008


Cum laude honors, Rector of Universitas Indonesia, Depok January, 1999
PUBLICATIONS


CONFERENCE PAPERS AND PRESENTATIONS


Pujasari, H. (2009, November). Nursing students 'and nurse educators' Perceptions and attitudes towards bioscience in an Indonesian Bachelor of Nursing program. Paper presented at The Third International Nursing Conference Jakarta Indonesia
