# THE ROLE OF DEPRESSION IN HIV TRANSMISSION AMONG PEOPLE WHO INJECT DRUGS IN VIETNAM

Sara N. Levintow

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Approved by:

Brian W. Pence

Vivian F. Go

Kimberly A. Powers

Carl A. Latkin

Stephen R. Cole

## ABSTRACT

Sara N. Levintow: The role of depression in HIV transmission among people who inject drugs in Vietnam
(Under the direction of Brian W. Pence)

The high incidence of HIV among people who inject drugs (PWID) demands closer examination of the drivers of transmission in this population. The burden of depression is high among PWID and may lead to persistent injecting behaviors, insufficient use of antiretroviral therapy (ART), and uncontrolled viremia. This dissertation study investigates the role of depression in transmission risk behaviors, ART initiation, and viral suppression, and models secondary transmission events among PWID in Vietnam, a key population in the country's HIV epidemic.

We analyzed data from 455 PWID living with HIV who enrolled in a randomized controlled trial of a prevention intervention in 2009-2013. Study visits every six months over two years measured depressive symptoms using the Center for Epidemiologic Studies Depression Scale (CES-D). Combining causal inference methods with mathematical modeling, we estimated the effect of depression as risk differences (RDs) in injection equipment sharing and condomless sex, cumulative incidence differences (CIDs) in ART initiation and viral suppression, and differences in total secondary transmissions projected to arise from participants.

The prevalence of severe depressive symptoms (CES-D ≥23) was 44% at baseline and 33% on average over follow-up. Severe depressive symptoms (vs. no or

mild symptoms) increased injection equipment sharing (RD = 3.9 percentage points, 95% CI: -1.7, 9.6) but decreased condomless sex (RD = -1.8, 95% CI: -6.4, 2.8) in the period three to six months later. Severe depressive symptoms lowered the cumulative incidence of ART initiation at six months (CID = -7.5, 95% CI: -17.2, 2.2) and 12 months (CID = -7.1, 95% CI: -17.9, 3.7), without appreciable differences in viral suppression. Across modeling analyses, the highest numbers of secondary transmissions were modeled for participants with severe depressive symptoms. However, there was substantial variability in model simulations due to the majority of transmissions arising from a small number of participants.

Future work probing these mixed findings for the effect of depression on sharing injection equipment (but not condomless sex) and on ART initiation (but not viral suppression) will inform the design of interventions for PWID and shed light on the extent to which successful depression treatment could avert future HIV infections.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AIDS | Acquired immunodeficiency syndrome |
| ART | Antiretroviral therapy |
| CD4 | Cluster of differentiation 4 |
| CES-D | Center for Epidemiologic Studies Depression Scale |
| CI | Confidence interval |
| CID | Cumulative incidence difference |
| EIA | Enzyme immunoassay |
| HIV | Human immunodeficiency virus |
| HPTN | HIV Prevention Trials Network |
| IQR | Interquartile range |
| MMT | Methadone maintenance treatment |
| MICE | Multiple imputation by chained equations |
| PWID | People who inject drugs |
| RD | Risk difference |
| RNA | Ribonucleic acid |

## CHAPTER I: SPECIFIC AIMS

Despite global progress in controlling the HIV epidemic, people who inject drugs (PWID) remain disproportionately at risk of HIV infection (1–3). Sharing drug preparation and injection equipment is one of the most efficient means of HIV acquisition and transmission (4,5), with injection drug use accounting for nearly one-third of HIV cases outside of sub-Saharan Africa (6,7). For PWID living with HIV, barriers to HIV care engagement and antiretroviral therapy (ART) use can inhibit viral suppression, resulting in onward HIV transmission to susceptible partners (8–10). Equipment sharing in the absence of viral suppression continues to sustain the HIV epidemic among PWID, particularly in Asia and eastern Europe (11,12).

Reducing injection behaviors and achieving widespread ART use present significant challenges (13–15), and the high burden of depression among PWID may be at the root of those challenges. Up to 50% of PWID suffer from severe depressive symptoms (16–20), and although not focused on PWID, a large body of research has linked depression to poor HIV treatment outcomes (18,21–32). There is also some evidence that depression promotes behaviors associated with transmission risk to injecting and sexual partners, such as sharing equipment and condomless sex (33–41). This combination of risk behaviors and uncontrolled viremia – potentially driven by depression – may then facilitate forward HIV transmission to susceptible partners. Despite these possible links, the role of depression in HIV transmission among PWID

has not been investigated, and the potential prevention impacts of depression interventions for PWID remain unknown.

The role of depression in HIV transmission among PWID is critical to investigate in Vietnam. Vietnam has one of the highest burdens of injection drug use worldwide, with an estimated 335,000 active PWID (42) and a history of societal marginalization and stigmatization of this vulnerable group (43,44). This study focused on 455 PWID who enrolled in a randomized controlled trial of an HIV prevention intervention in Thai Nguyen, Vietnam from 2009 to 2013 (45). In the trial, depression was assessed with the Center for Epidemiologic Studies Depression Scale (CES-D) (46), a measure of current symptoms widely used among PWID (47–49) and validated in Vietnam (50,51). Our prior work found that nearly half of trial participants experienced severe depressive symptoms (20), and in this study, we investigated the role of depression in HIV transmission by addressing the following three aims:

**Aim 1: Estimate the association of depression with transmission risk behaviors.** Questionnaires implemented every six months over two years assessed injection equipment sharing and condomless sex in the past three months. Previous studies of the relationship between depression and these behaviors have been unable to infer causality, as they have evaluated only the cross-sectional association between contemporaneously assessed depression and behaviors and have not accounted for the episodic nature of depression and confounders. We sought to overcome past methodological issues by using a causal approach that incorporated the episodic nature of depression and controlled for time-varying confounders. We hypothesized that

depression among PWID with HIV increased both injection equipment sharing and condomless sex over two years of follow-up.

**Aim 2: Estimate the association of depression with ART initiation and viral suppression.** At each trial visit, data were collected on physician- and self-reported ART use, and to obtain viral load data for this study, we performed HIV RNA testing on stored plasma specimens. Although an inverse relationship between depression and HIV treatment outcomes has been established, prior work has not focused on PWID; studies have been conducted among clinical cohort patients who were engaged in HIV care. This analysis provides insights into the association between depression, ART initiation, and viral suppression specifically in the PWID population, with most participants not in care at the start of follow-up. We hypothesized that PWID with depression had lower cumulative incidences of ART initiation and viral suppression, compared to PWID without depression.

**Aim 3: Quantify the overall role of depression in HIV transmission by modeling secondary HIV transmission among PWID.** We developed a mathematical model that combined behavioral and viral load data to estimate secondary HIV transmission events from PWID to their potentially susceptible injecting partners. While prior research has focused on individual components of transmission risk (e.g., behaviors or viral load), this model is the first to investigate the overall contribution of depression to HIV transmission through the combination of behavioral and biological pathways. We hypothesized that greater secondary transmissions during the study period would be estimated for PWID with depression, compared to those without depression.

This study combined causal inference methods with mathematical modeling to better understand the HIV epidemic and guide control efforts among PWID with HIV in Vietnam. The population impact of HIV prevention efforts will be compromised if the underlying causes of transmission are not addressed. Depression screening and treatment may be critical to reducing risk behaviors, increasing viral suppression, and ultimately, slowing forward transmission in a key population in the HIV epidemic.

## CHAPTER II: BACKGROUND

The HIV epidemic contributes to substantial morbidity and mortality worldwide, resulting in 78 million infections and 35 million deaths to date (52–54). For people living with HIV, ART is successful in controlling viral replication, slowing progression to AIDS, and reducing risk of HIV transmission (55,56). However, there remain significant global disparities in controlling the epidemic; a particularly vulnerable group are PWID (1,3,6). HIV can be spread if certain bodily fluids (e.g., blood) from a person with HIV come into contact with a mucous membrane or damaged tissue or directly enter the bloodstream, making the sharing of injection drug use equipment one of the most efficient means of HIV transmission (4,5). Because most PWID with HIV have limited access to and insufficient use of harm reduction services and ART (2,9,10), injection drug use and viremia often persist, resulting in a high risk of HIV transmission to injecting or sexual partners (8–10). The combination of equipment sharing in the absence of viral suppression results in continued HIV incidence among PWID, particularly in southeast Asia, central Asia, and eastern Europe (11,12).

In Vietnam, HIV prevalence has risen above 30% among PWID in several provinces (57–59). Although PWID make up nearly half of HIV cases in Vietnam, they account for very few patients on ART (13). PWID in Vietnam experience multi-level barriers to ART access and adherence; qualitative work has shown that these include ongoing drug use and withdrawal symptoms, lack of social support, anticipated stigmatization from providers, financial burden, and limited clinic access (60). There is

an urgent need for prevention programs to facilitate ART use for PWID living with HIV and reduce transmission to partners, as reflected in recent HIV prevention trials assessing the feasibility of future interventions for PWID in Vietnam (61). Risk reduction and viral suppression are both critical components of combination HIV prevention (15,55), but their success among PWID relies on addressing barriers unique to this population.

Vietnam has one of the highest burdens of injection drug use worldwide, with an estimated 200,000-300,000 PWID (7,42) and a history of societal marginalization and stigmatization of this vulnerable group (43,44). In the early 2000s, government policies to address drug use in Vietnam grew repressive and punitive, instituting compulsory detoxification and detention facilities known as “06 centers.” From 2006 to 2010, there were 169,000 admissions to 06 centers, where residents encountered crude attempts at detoxification, “moral education”, and forced labor (62). This stigmatization of injection drug use hindered the efforts of policy leaders and healthcare workers in advocating for and implementing evidence-based harm reduction interventions (63). Beginning in 2008, substance use treatment policy in Vietnam began to shift, as pilot programs for methadone maintenance demonstrated significant impacts on relapse rates (64) in addition to improved healthcare utilization and cost effectiveness (65). The government committed to expansion of the methadone maintenance program, and in 2013, formally recognized drug addiction as a chronic condition due to both biological and psychosocial causes, rather than simply a “social evil.” With this commitment to evidence-based addiction treatment, the government has taken steps to reduce 06 centers; in 2015, the number of residents had fallen to 15,500 (63).

Despite transitioning to a more progressive approach on drug use in recent years, Vietnam's history of punitive policies and severe stigmatization have deterred PWID from accessing health services, such as HIV testing and treatment. This group is difficult to reach for intervention (13), and even when PWID do enter care, simply offering ART is insufficient for successful HIV treatment and prevention. A substantial proportion continue to engage in (or relapse to) injection drug use without achieving viral suppression (66). Insufficient adherence to ART is common and can lead to treatment failure and development of drug resistance (67–69). This persistence of injecting behaviors, limited engagement in HIV care, and poor adherence to ART have significant implications for continued HIV spread among PWID, particularly due to the high transmission probability of parenteral exposure (4). In order for prevention efforts to be successful, these challenges to risk reduction and viral suppression must be addressed, and the mental health of PWID may be at the root of these challenges.

The burden of depression is high among PWID and may interfere with HIV prevention efforts. Depression (also known as major depressive disorder or clinical depression) is characterized by symptoms of sadness, hopelessness, loss of interest or pleasure, feelings of guilt or low self-worth, sleep and appetite disruptions, fatigue, and poor concentration (70). In Vietnam, the translation and clinical term for depression is trầm cảm, and qualitative work in Vietnam has found that ART clients conceptualize depression primarily as a loss of social support, acute stigma and isolation, and suicidal thoughts (71). In Vietnam and other areas, depression has been found to be exceedingly common among PWID (16–20). In our prior work in Vietnam, we found that 44% of PWID living with HIV reported severe depressive symptoms (20) as assessed

with the CES-D (46). The CES-D is a measure of current depressive symptoms widely used among PWID (47–49) and validated in Vietnam (50,51). Although not a clinical diagnostic, a score of 16 or greater indicates probable depressive symptoms in the general population, with higher cut-points used for patients with comorbid chronic illness, such as HIV (50); notably, our study used a conservative cut-point of 23 to indicate severe depressive symptoms. This estimate of 44% is considerably higher than pooled prevalence estimates of depression for people living with HIV that range from 13% to 24% (72) and global estimates that 4.4% of the world's population suffers from depression (73).

The relationship between depression and injection drug use is complex. There is evidence that depression is a risk factor for injection drug use (74,75) and that depressive symptoms may be substance-induced (76) or a consequence of stigma and isolation experienced by PWID (77). Regardless of whether depression precedes or results from drug use, its presence and severity are closely linked to frequency of injection and risks of relapse or remission (48,74,78). This interconnected nature of depression and injection drug use fits into the broader psychological framework that depressed mood manifests as cognitive distortions, maladaptive coping, and loss of risk aversion (79). These symptoms of depression may then facilitate the "perfect storm" of behavioral and biological conditions that enable HIV transmission to occur.

Although not focused on PWID, a large body of research shows that depression consistently results in worse HIV outcomes for people living with HIV and depression, compared to those without depression (18,21–32). Depression has been linked to lower initiation of and adherence to ART (21–23), poorer attendance at HIV care visits (30),

decreased CD4 cell count (18,23,26), higher viral load (23,24,26,28,30,31), and greater risk of mortality (29,32). There is also some evidence that depression promotes behaviors associated with transmission to injecting and sexual partners, such as sharing injection equipment and condomless sex (33–41). This combination of ongoing behaviors and uncontrolled viremia – potentially driven by depression – must be addressed to slow the spread of the epidemic among PWID and susceptible partners.

While depression is recognized as a high burden among people living with HIV, the extent to which depression treatment could prevent future HIV spread is not well understood. There are numerous evidence-based pharmacologic and psychotherapeutic approaches for treating depressive symptoms (80), and among people living with both HIV and depression, depression interventions have included antidepressant medication, cognitive behavioral therapy, and problem solving therapy (79,81–87). To date, few studies have examined the effect of depression treatment on injecting and sexual behaviors (79,85), none among PWID with HIV. There is accumulating evidence that depression treatment can promote adherence to antiretroviral therapy and viral suppression (81–84). Improving our understanding of the role of depression in HIV transmission will lay the groundwork for future research on depression treatment among PWID and potential impacts on HIV transmission. Historically, mental health services in Vietnam have focused on schizophrenia and other conditions treated in inpatient settings, but there is growing attention and funding for increasing local services and the availability of treatment outside of inpatient settings (88,89). Depression is a prioritized condition in Vietnam (88), and improved access to

depression treatment has the potential to confer important benefits in terms of both mental health and HIV prevention.

**Significance**

Controlling the HIV epidemic among PWID may require addressing depression as an underlying cause of uncontrolled viremia and ongoing behaviors that result in transmission to injecting or sexual partners. Prior studies have found that depression is exceedingly common among PWID and is associated with poor HIV outcomes; however, the current research lacks a unified perspective that considers these individual associations together and assesses the overall effect of depression on onward transmission. Persistent injecting and sexual behaviors in conjunction with low viral suppression are the key drivers of forward HIV spread. Yet, no prior study has combined empirical data on both behaviors and viral load to investigate how depression may facilitate these conditions for HIV transmission to occur. If depression is fueling the HIV epidemic among PWID, then the recognition and treatment of depressive symptoms is imperative, not only for health outcomes of PWID, but for slowing the spread of HIV to susceptible partners.

This study represents an important step to better understanding and controlling the HIV epidemic among PWID. To build on prior research, we used causal inference methods to estimate the associations of depression with transmission risk behaviors, ART initiation, and viral suppression for PWID living with HIV in Vietnam. By developing a mathematical model, we estimated secondary HIV transmission events from PWID to their potentially susceptible partners and quantified the overall role of depression in forward transmission. Given continued HIV incidence among PWID and the plausible

role of depression therein, it is critical to better understand how depression may drive onward transmission and the extent to which successful depression treatment could avert future infections.

**Innovation**

This study is an innovative approach, combining causal inference methods with mathematical modeling to quantify the role of depression in promoting injecting and sexual behaviors, hindering ART initiation and viral suppression, and ultimately contributing to forward HIV transmission among PWID in Vietnam, a key population in the country's HIV epidemic.

In Aim 1, we used a causal approach to overcome past methodological issues in estimating the effect of depressive symptoms on the injecting and sexual behaviors that can facilitate HIV transmission or acquisition. To our knowledge, all previous studies have assessed only correlations between depression and behaviors (without inferring causality) and have not accounted for the episodic nature of depression and confounders (33–41). Potentially due to these methodological issues, existing evidence for associations between depression and transmission risk behaviors has been inconsistent. In this study, we used marginal structural models, a tool for causal inference that controlled for time-fixed and time-varying confounders (90–92); this modeling approach also temporally separated depression from behaviors and accounted for the episodic nature of depression. With this innovative approach, we sought to advance our understanding of the role of depression in HIV transmission through its effect on behavior.

In Aim 2, we expanded upon pre-existing research linking depression to poor HIV treatment outcomes (18,21–32) by investigating these associations in the PWID context. A large body of literature has found lower ART initiation and viral suppression in clinical cohorts of HIV patients engaged in care, with little (if any) ongoing injection drug use. In contrast, the majority of our study population was not in care at the start of follow-up and all reported current injection drug use. Thus, our analysis provides insights into the association between depression, ART initiation, and viral suppression outside of well-established clinical cohorts and specifically among PWID.

In Aim 3, the development of a mathematical model of HIV transmission among PWID is novel. HIV spread through sexual transmission has been the focus of previous modeling work, with fewer studies exploring the contribution of injection drug use to the epidemic (14,15,93–98) We developed a Bernoulli process mathematical model to estimate the expected number of secondary HIV transmission events from study participants (99), incorporating each participant's specific behaviors, numbers of partners and acts within those partnerships, and transmission probability given viral load. Previously developed Bernoulli models among PWID used little empirical data and instead relied on simplistic and likely inappropriate assumptions, such as assuming a constant probability of transmission regardless of behavior type or an individual's stage of infection (93). In contrast, our model used behavior and viral load data measured directly from the study population to account for realistic heterogeneity in HIV infectiousness.

Using this model, our study is the first to quantify the role of depression in ongoing HIV transmission among PWID. Although a large body of research has studied

depression and individual components of transmission risk (e.g., behaviors or viral load), this model is the first to investigate the net contribution of depression to HIV transmission through the combination of behavioral and biological pathways. The output of Bernoulli models (the expected number of onward transmission events per individual) is a useful and meaningful quantity, with a history of informing HIV prevention efforts (100). Contrasting model estimates by depression enables us to quantify the potential excess transmission predicted for participants with depression. These estimates of secondary transmission also lay the groundwork for future modeling work that projects the potential HIV prevention benefits (i.e., numbers of infections averted) that could be achieved through depression interventions among PWID.

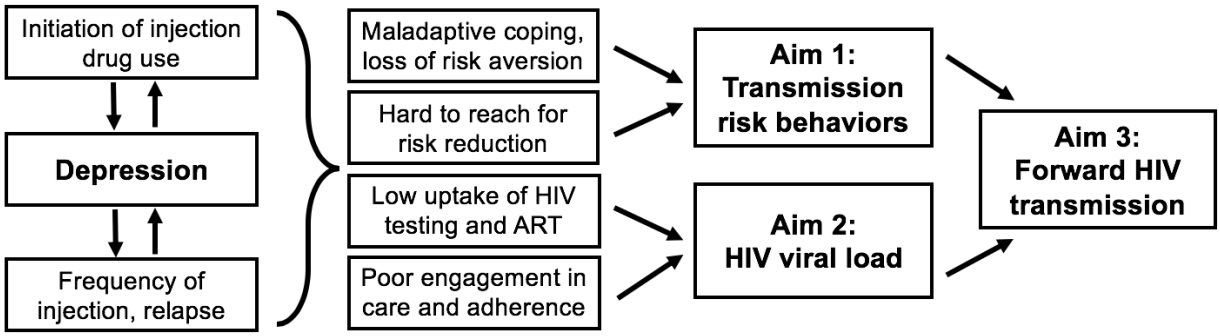
# CHAPTER III: METHODS

## Overview

The overall goal of this study is to investigate the role of depression in HIV transmission among PWID in Vietnam. Longitudinal data from a randomized controlled trial of an HIV prevention intervention among PWID in Vietnam were used to estimate the effect of depression on transmission risk behaviors (Aim 1), ART initiation and viral suppression (Aim 2), and secondary HIV transmission events (Aim 3).

Figure 3.1 depicts the conceptual model underlying all methods for this study. In Aims 1 and 2, we estimated the effect of depression on the key determinants of HIV transmission: behaviors and viral load. We hypothesized that in the context of injection drug use, depressive symptoms manifest as maladaptive coping and loss of risk aversion, resulting in a higher likelihood of sharing injection drug use equipment and engaging in condomless sex, while also making this group difficult to reach for interventions to change these behaviors. In addition, depressive symptoms were hypothesized to decrease health-seeking behaviors, which hindered engagement in HIV care and medication adherence, resulting in unsuppressed viremia. For Aim 3, we used data on both behaviors and viral load to estimate secondary HIV transmission events, hypothesizing that depression led to excess transmission through the combination of these behavioral and biological pathways.

**Figure 3.1. Conceptual model of dissertation study aims.**




## Parent Trial

This dissertation study was nested within a randomized controlled trial of a multi-level HIV stigma and risk reduction intervention that enrolled PWID living with HIV in Thai Nguyen, Vietnam from 2009 to 2013 (known as the "Prevention for Positives" trial; ClinicalTrials.gov identifier: NCT01689545). Thai Nguyen is a province in northeastern Vietnam with an estimated HIV prevalence of 34% among its approximately 6,000 PWID (57–59). Out of 180 sub-districts in Thai Nguyen, participants were recruited via snowball sampling from the 32 sub-districts with the most PWID. Recruiters (former and current PWID) approached members of drug networks in private places to discuss study enrollment and then accompanied or referred interested participants to the study site for screening. At screening, participants were tested for HIV using two rapid EIA tests run simultaneously (Determine: Abbot Laboratories, Abbott Park, IL and Bioline: SD, Toronto Canada), with discordant results resolved with a third rapid assay (HIV Rapid Test: ACON, San Diego, CA).

Enrolled participants met the following eligibility criteria: 1) HIV-positive (confirmed through study testing), 2) male (because 97% of PWID in Thai Nguyen are

male, and females would require a different intervention), 3) age ≥18 years, 4) reported having sex and injecting drugs in the prior six months, and 5) planned to live in Thai Nguyen for the next 24 months.

A two-stage process was used to randomize the 32 sub-districts of participants to a structural-level intervention and to randomize the 455 participants across sub-districts to an individual-level intervention (45). This process resulted in four trial arms to which participants could belong: 1) control (standard of care), 2) individual (individual intervention only), 3) sub-district (sub-district intervention only), and 4) combined (individual and sub-district interventions).

The sub-district intervention aimed to reduce community-level HIV and injection drug use stigma, and the individual intervention sought to support participants in coping with HIV and reducing transmission risk behaviors. Sub-districts randomized to the structural-level intervention received a community-wide program consisting of a video screening and series of HIV education sessions, while sub-districts assigned to standard of care received standard messaging through educational pamphlets and public loudspeakers. Participants randomized to the individual-level intervention received enhanced HIV post-test counseling and group support sessions; those assigned to standard of care were delivered HIV testing and counseling in accordance with current Vietnamese guidelines. At the trial start in 2009, national eligibility criteria for ART were CD4 cell count ≤200 cells/$\mu$l and had moved to CD4 cell count ≤350 cells/$\mu$l by the end of the trial in 2013 (101,102).

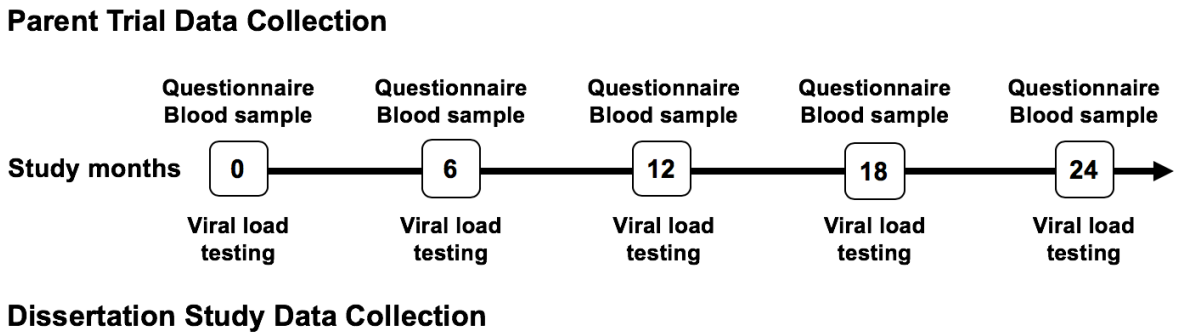
## Study Population

Out of 2,136 people approached for trial recruitment in Thai Nguyen, 1,739 were screened for eligibility, and among those screened, 455 participants were enrolled and completed the baseline visit (1,215 were not eligible, and 69 did not attend the baseline visit or otherwise refused to participate). Follow-up visits took place at 6, 12, 18, and 24 months following baseline. At each visit, a structured questionnaire was administered, and participants were asked to provide blood specimens to assess CD4 cell count. Written informed consent was obtained from all eligible participants at screening and enrollment, and at baseline and follow-up visits, participants were reimbursed 75,000 Vietnamese Dong ($3.50 USD) plus 5,000 Vietnamese Dong ($0.23) per kilometer traveled.

## Measures

At each visit, the questionnaire was administered by a trained interviewer face-to-face in a private room at the project facility and took approximately 1-1.5 hours to complete. Key variables for this dissertation study from the questionnaire were demographics, injection drug use and other substance use, sexual behavior, depression, quality of life, and ART use. In addition to the questionnaire data, this dissertation study used measures of CD4 cell count and viral load from blood specimens and physician reports of participants' ART use. Data collection methods for this study are shown in Figure 3.2.

**Figure 3.2. Sources and frequency of data collection for parent trial and dissertation study.**




## Depression

As part of the questionnaire at each visit, the CES-D was administered to assess depressive symptoms over the past week. The CES-D contains 20 items comprising six scales, each corresponding to a major aspect of depression: depressed mood, feelings of guilt or worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance (46). The respondent is asked to rank each item according to how often they felt or behaved that way over the past week, with four options ranging from “Rarely or none of the time (less than 1 day)” to “Most or all of the time (5-7 days).” Each item receives a score of 0, 1, 2, or 3, with higher scores reflecting greater symptomatology, and item scores are summed to calculate the total score, ranging from 0 to 60. The CES-D has been widely used among PWID to assess depression (47–49) and has been validated in Vietnam (50,51). Although not a clinical diagnostic, scores of ≥16 have been found to indicate probable depressive symptoms in the general population (46), and higher cut-points are used for patients with comorbid chronic illness, such as HIV (50).

For the main exposure of interest across Aims 1-3, we used CES-D scores to categorize participants by depressive symptom severity. Consistent with past work (20,46,50,51), we defined severe depressive symptoms as CES-D scores ≥23, mild depressive symptoms as scores 16-22, and no symptoms as scores <16.

**Injecting Behavior**

In the questionnaire, participants reported injection drug use from the prior three months. Participants were asked about the type of drug most frequently injected, the number of days during the past three months they injected that drug, and if they had ever overdosed. Participants were also asked about injection equipment sharing with injecting partners over the last three months, with an injecting partner defined as someone in the same room as or in close proximity to the participant when they were both injecting drugs. Participants reported a global measure of injection equipment sharing across all partners from the prior three months (any/none), in addition to detailing types and numbers of sharing behaviors per injecting partner (for up to 10 partners). Specifically, for each partner, participants were asked to report the frequency in those three months of: 1) sharing the same needle or syringe, 2) sharing drug solution, and 3) sharing the same ampoule of distilled water or novocaine. Participants were also asked if each partner had HIV, with possible responses being “Yes”, “No”, or “Don’t know”.

To estimate the effect of depression on transmission risk behaviors in Aim 1, the global measure of injection equipment sharing (i.e., any/none in the prior three months) was used as one of the primary outcomes (in addition to condomless sex). This global measure was also included in Aim 2 as a potential confounder of the relationship

between depression, ART initiation, and viral suppression. To model secondary transmissions in Aim 3, we used the partner-specific measures of types and numbers of sharing acts.

**Sexual Behavior**

Participants were asked if they had sex with a male or female partner without using a condom in the prior three months. Similar to the global measure of injection equipment sharing, this measure of condomless sex (i.e., any/none in the last three months) was used as a primary outcome for Aim 1 and included as a potential confounder in Aim 2.

**ART Use**

As part of the questionnaire at each visit, participants were asked if they were currently taking ART, and in addition, participants were seen by the study physician who also ascertained current ART use. The outcome of ART initiation for the Aim 2 analysis was defined based on both participant- and physician-reported data. A participant was considered to have initiated ART in the prior six months as of the first visit at which the study physician reported participant ART use. If the physician's report of ART use was missing (occurring for 17% of study visits overall), we used the participant's report of ART use in the previous six months. In prior work in this population, we found 92% concordance between participant- and physician-reported ART use (103).

**Viral Load**

In the parent trial, blood specimens were collected to confirm HIV infection at baseline and measure CD4 cell count at all visits. Because viral load was not originally measured, this study performed HIV RNA testing on stored blood plasma specimens

using COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test platform (Roche Diagnostics GmbH) with a lower limit of detection of 20 copies/mL. The viral load data was incorporated into the transmission model in Aim 3 and was used to define the outcome of viral suppression for the Aim 2 analysis. Participants were considered to have experienced the viral suppression outcome as of the first visit with viral load <400 copies/mL. This cut-point was chosen given prior work showing that HIV transmission is highly unlikely when viral load is <400 (104).

**Other Covariates**

Potential confounders included in the Aims 1-2 analyses were marital status (single, married or cohabitating, separated, divorced or widowed), age (in years), employment status (full-time, part-time, unemployed), history of overdose (yes/no), current alcohol use (yes/no), HIV diagnosis prior to enrollment (yes/no), CD4 cell count category (<200, 200-349, 350-499, ≥500 cells/μL), and intervention arm (Control, Individual, Subdistrict, Combined).

**Competing Events**

Study outreach workers attempted to trace participants who missed a follow-up visit (at 6, 12, 18, 24 months) using the contact information collected at baseline. During tracing procedures, outreach workers asked participant contacts if the participant had died or was incarcerated. These measures of death and incarceration were included as competing events across Aims 1-3.

**Data Analyses**

The analytic approaches for all study aims were motivated by the episodic nature of depression. The presence and severity of depressive symptoms changed over time in

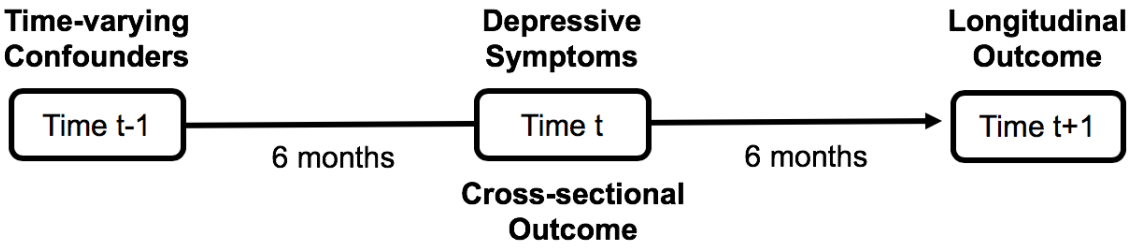
the study population, as reflected by variability in CES-D score across 24 months. Rather than relying on a single measure of depressive symptoms, each analysis incorporated assessments from multiple time points to more fully capture the relationships between depression and the outcomes of interest.

All analyses were conducted using R Version 3.4.3 (105). See Appendix 1 for R packages used in analyses.

**Aim 1 Analysis**

To estimate the effect of depression on transmission risk behaviors, we used marginal structural models, a method for causal inference used for time-varying exposures and controls for time-varying confounders (90–92,106). In the main analysis, we estimated the average causal effect of severe depressive symptoms (vs. mild or no symptoms) on the risks of any injection equipment sharing or any condomless sex (separately) in the period three to six months later. We evaluated each risk behavior outcome (reported with respect to the prior three-month period) at the next six-month visit in order to temporally separate it from the exposure of depressive symptoms (hereafter referred to as the "longitudinal effect"). In a second analysis, to facilitate comparison with prior research, we estimated the association between depressive symptoms and risk behaviors reported at the same visit, where their temporal ordering could not be differentiated (referred to as "cross-sectional association"). In all models, we controlled for time-varying confounders using the value from the visit immediately preceding the visit at which depressive symptoms were assessed. This modeling approach is depicted in Figure 3.3.

**Figure 3.3. Aim 1 marginal structural modeling approach.**




We used inverse probability weighted estimation of marginal structural models (90,107). The weights were estimated from a propensity score model for the probability of severe depressive symptoms at each visit as a function of time-fixed and time-varying confounders, identified prior to analysis. Time-fixed confounders had a constant (baseline) value over all visits and included marital status, age, employment status, intervention arm, history of overdose, current alcohol use, HIV diagnosis prior to enrollment, and history of ART use. Time-varying confounders measured at one time point may affect subsequent depression and risk behaviors; they may also be influenced by depression and risk behaviors from a previous time point. Thus, time-varying covariates may act as either confounders or mediators, depending on the time point assessed (90,108). For this analysis, time-varying covariates were CD4 cell count category, history of depressive symptoms, and history of transmission risk behaviors, using the value from the visit prior to the assessment of depressive symptoms.

In the main analysis, the propensity score model was estimated using logistic regression to model the probability of severe (vs. mild or no) depressive symptoms. In secondary analyses, we used ordinal logistic regression to separately model the three levels of depressive symptoms (severe vs. mild vs. none). Application of the weights to

the study population removes the association between depressive symptoms and the potential confounding variables included in the propensity score model, permitting estimation of a causal effect under the key assumptions of consistency, conditional exchangeability, positivity, and no model misspecification (107,109). In the weighted study population, we estimated the RD for the risk behavior outcomes using generalized estimating equations to account for repeated observations on participants (110–112). For the longitudinal analysis, this weighted RD can be interpreted as the causal effect of depressive symptoms on the risk behavior outcome: that is, the difference in risk of the behavior in the period three to six months later if all participants had depressive symptoms compared with the risk if they all did not have depressive symptoms.

To account for missing data due to missed study visits, we used multiple imputation by chained equations (MICE) for all variables included in the analysis (113,114), imputing and analyzing 50 datasets. We included participants who were incarcerated or had died during the study period in the main analysis up until the six-month follow-up interval during which the competing event occurred, censoring them at that interval. In sensitivity analyses, we instead used the imputed risk behavior outcome for that six-month interval (and censored them at the following interval), given the possibility of engaging in unmeasured risk behaviors prior to incarceration or death.

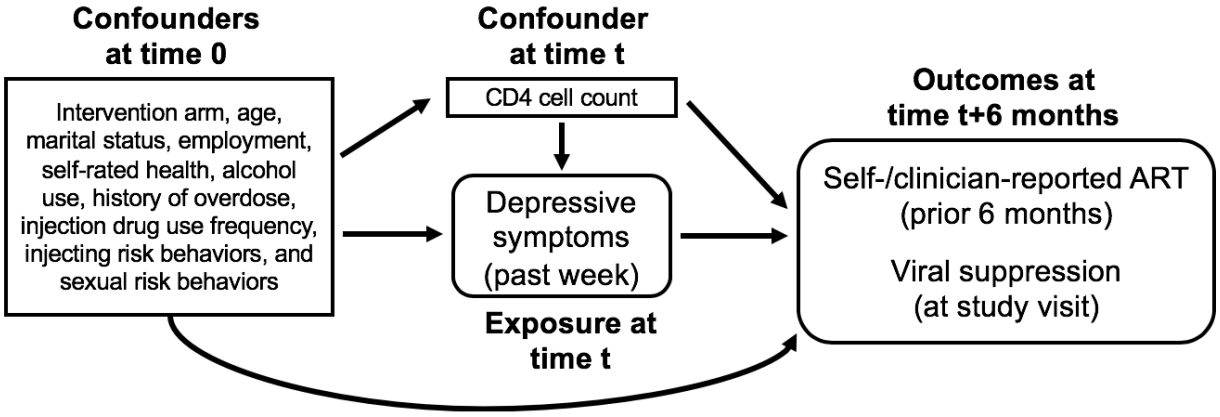
**Aim 2 Analysis**

We also used inverse probability weighting to account for the time-varying nature of depression in our analysis of ART initiation and viral suppression. Specifically, we used a semi-parametric inverse probability-weighted estimator of the 6- and 12-month cumulative incidence of ART initiation and viral suppression (analyzed separately)

under three scenarios: 1) Natural course: the incidence of the outcome in the observed study population, 2) Never depressed: the incidence of the outcome if participants never had severe depressive symptoms (i.e., symptoms were mild or absent, defined as CES-D score <23, at all study visits up to and including the visit prior to outcome ascertainment), and 3) Always depressed: the incidence of the outcome if participants always had severe depressive symptoms (CES-D ≥23 at all study visits up to and including the visit prior to outcome ascertainment). Death and incarceration were treated as competing rather than censoring events for the outcomes of interest.

We estimated cumulative incidence under the never-depressed and always-depressed scenarios by weighting participants who never had severe symptoms and who always had severe symptoms, respectively, to represent the full study population in terms of potential confounders of the relationship between depression, ART initiation, and viral suppression. These hypothesized confounders included marital status, age, employment status, intervention arm, CD4 cell count, self-rated general health, recent alcohol use, history of overdose, frequency of injection drug use, recent sharing of injection equipment, and recent condomless sex. The causal diagram summarizing these hypothesized relationships is provided in Figure 3.4.

**Figure 3.4. Directed acyclic graph with hypothesized associations for key variables in Aim 2.**




As in Aim 1, application of the weights to the study population removes the association between the potential confounding variables included in the model and depressive symptoms, permitting estimation of a causal effect between depression and our outcomes of interest under key assumptions of consistency, conditional exchangeability, positivity, and no measurement error (107,109). In the weighted study population, we estimated the cumulative incidence of each outcome at 6 and 12 months as the cumulative sum of the weights for participants experiencing the outcome, divided by the total sample size. To ensure that depression occurred prior to the outcome, outcomes lagged their assigned weight values by 6 months (i.e., baseline weight values were used for outcomes at 6 months; 6-month weight values were used for outcomes at 12 months). We estimated the CID contrasting the never-depressed and always-depressed scenarios: that is, the difference in 6- and 12-month cumulative incidence of the outcome (ART initiation, viral suppression) if participants always had severe

depressive symptoms, compared with the risk if participants never had severe depressive symptoms.

We focused on cumulative incidence estimates at 6 and 12 months (rather than the full 24-month follow-up period) due to substantial missing data on viral load. This missingness was due to insufficient sample volume (<1mL) for 31% of specimens at 6 months, 59% at 12 months, 48% at 18 months, and 55% at 24 months. To limit the influence of missing data, we evaluated both outcomes of interest only at the two earliest follow-up visits (6 and 12 months). Similar to Aim 1, we used MICE to analyze 50 complete datasets with values imputed for missing viral load and other study variables with intermittent missing data not due to death or incarceration (<15% across all variables at all visits) (113,114). Rubin's formula was used to pool results and calculate variance accounting for within- and between-imputation variability (113).

**Aim 3 Analysis**

Combining behavioral and viral load data from Aims 1 and 2, we developed a modified Bernoulli process mathematical model (99,115–118) to estimate the parenteral HIV transmissions from each study participant in two periods: the three months before baseline and the three months before the six-month visit. Transmission estimates were based on viral load measurements taken at the end of a given period, reported numbers of injecting partners in the period, sharing acts within those partnerships over the specified period, and reported partner HIV status. We limited the scope of our analysis to data collected at the baseline and six-month follow-up visits due to substantial missing data on viral load at the 12-, 18-, and 24-month visits.

For each named partner in a specified period, we estimated the probability that the participant would transmit HIV to that partner as a function of the probability that the partner was already HIV-infected, the number of acts between the participant and partner over the period, and the probability of HIV transmission in one sharing act with a susceptible partner. This per-act transmission probability was calculated as a function of the participant's viral load. For each participant, we then summed across the partner-specific probabilities to obtain the total number of secondary transmissions estimated for that participant in a given three-month period.

Our model parameters came from both the observed data and published estimates from the scientific literature (Table 3.1). The number of sharing acts and the probability of partner HIV infection were based on questionnaire reports at baseline and six months. For the probability of HIV infection among partners whose HIV status was reported as unknown, we used an estimate of overall HIV prevalence (34%) among PWID in Thai Nguyen during the study period (57–59). Participant viral load was fully observed at trial baseline, and for missing viral load due to insufficient samples at six months (31% of participants), we used MICE (113,114) to impute viral suppression status and assign viral load. To derive the per-act transmission probability using participant viral load, we relied on prior transmission estimates (119–121) for the average viral load set-point, transmission probability per sharing act at that set-point, and increase in infectiousness per $\log_{10}$ increase in viral load above the set-point value. Further details about these model parameters are included in Chapter VI.

To evaluate differences in predicted transmission events by depression, we stratified the population according to baseline depressive symptoms (severe, mild, or no

symptoms) and compared the total number of estimated transmissions by depressive symptom group, the probability of infection per partner, and the number of estimated transmissions per participant. To account for different sample sizes by depression, we weighted the number of total transmissions such that each group was upweighted to stand in for the full study population.

**Table 3.1. Observed and estimated Bernoulli model parameters for Aim 3**.

| Model Parameter | Estimate | | Source |
|---|---|---|---|
| Number of sharing acts with partner | Participant-reported frequency category | Assigned count per 90 days | Trial data Literature (122) |
| | Never | 0 | |
| | <1 time a month | 1.5 | |
| | 2-3 times a month | 7.5 | |
| | 1 time a week | 12 | |
| | 2-3 times a week | 30 | |
| | Everyday | 90 | |
| Probability of pre-existing HIV infection for partner | Participant-reported partner HIV status | Assigned probability of HIV infection | Trial data Literature (58,59) |
| | HIV-positive | 1 | |
| | HIV-negative | 0 | |
| | Unknown | 0.34 | |
| Participant's HIV viral load | Observed copies/ml with multiple imputation of viral suppression status where missing: | | Trial data |
| | Impute suppression | Randomly assign viral load 1-400 | |
| | Impute no suppression | Carry forward baseline value (>400) | |
| Viral load set-point | $\log_{10}$ 4.5 copies/ml | | Literature (119) |
| Transmission probability at viral load set-point | 0.008 (range 0.0063-0.024) | | Literature (120) |
| Rate ratio per log10 increase in viral load | 2.09 (95% CI 1.47, 2.97) | | Literature (121) |

# CHAPTER IV: ESTIMATING THE EFFECT OF DEPRESSION ON HIV TRANSMISSION RISK BEHAVIORS AMONG PEOPLE WHO INJECT DRUGS IN VIETNAM: A CAUSAL APPROACH

## Introduction

Despite global progress in combating the HIV epidemic, PWID remain disproportionately at risk of HIV infection (1–3). Sharing injection equipment is an efficient means of HIV transmission (4,5), and high HIV incidence continues among PWID, particularly in southeast Asia, central Asia, and eastern Europe (11,12). Because PWID have limited access to and insufficient use of harm reduction services and ART (9,10), injection drug use and viremia often persist, resulting in a high risk of HIV transmission to injecting or sexual partners (8).

Persistent risk behaviors and lack of HIV treatment engagement may be driven – at least in part – by a high burden of depression among PWID. Up to 50% of PWID suffer from severe depressive symptoms (16–20), and comorbid depression consistently results in poor HIV treatment outcomes (21,25–29). By lowering ART uptake and viral suppression, depression may also be an important driver of continued HIV incidence among PWID. However, while the deleterious effect of depression on HIV care and treatment engagement is well established, its effect on the injecting and sexual behaviors that can facilitate HIV transmission or acquisition is not well understood.

Existing studies on depression and HIV transmission risk behaviors among PWID have suffered from several methodological limitations. To our knowledge, all previous studies have assessed only correlations between depression and transmission risk

behaviors, without inferring causality (33–41). In these studies, depression and risk behaviors have typically been evaluated for the same time period (e.g., self-report covering the last month), without the ability to infer whether depression preceded risk behaviors or vice versa (36–38,40,41). Potential confounders of the relationship between depression and risk behaviors were also measured for the same retrospectively assessed time period. Studies that used traditional statistical adjustment for these contemporaneous covariates (35,39) may have induced bias if these variables acted as causal mediators rather than confounders (108). In addition, although depression is known to be episodic (123), prior analyses have primarily relied on a single assessment rather than accounting for changes in both depressive symptoms and time-varying confounders (34,35,39,41).

Possibly stemming from these methodological issues, existing evidence for an association between depression and transmission risk behaviors is inconsistent. While an early meta-analysis found little evidence for an association between depression and sexual risk behaviors (33), more recent studies have found higher sexual risk associated with depression (35,36,41) or a non-linear association (37) in which mild symptoms are most predictive of sexual risk. The few studies that have evaluated the association of depression with injecting risk behaviors have suggested that depressive symptoms were associated with greater injecting risk behaviors (36,38–40).

Our study sought to overcome past methodological issues by using a causal approach to estimate the effect of depressive symptoms on transmission risk behaviors. We used marginal structural models, a tool for causal inference that controls for time-fixed and time-varying confounders (90–92). Our modeling approach also temporally

separated depression from risk behaviors and accounted for the episodic nature of depression. Data for this study came from PWID living with HIV in Vietnam who reported behaviors associated with risk of HIV transmission to injecting partners (sharing injection drug use equipment) and sexual partners (condomless sex). We hypothesized that depression increased both injection equipment sharing and condomless sex over two years of follow-up. Through a methodologically rigorous investigation, we aimed to study depression as a potential underlying cause of HIV transmission and to provide clearer evidence to inform interventions against depression to avert future HIV infections among PWID.

## Methods

### Parent Trial Design and Population

We used longitudinal data from a randomized controlled trial of a HIV stigma and risk reduction intervention among PWID living with HIV in Thai Nguyen, Vietnam from 2009-2013 (45). The trial enrolled 455 participants who met the following eligibility criteria: 1) confirmed HIV diagnosis, 2) male (given that 97% of PWID in Thai Nguyen are male), 3) age ≥18 years, 4) had sex in the past six months, 5) injected drugs in the previous six months, and 6) planned to live in Thai Nguyen for the next 24 months.

### Measures

Questionnaire and laboratory data were collected at study visits every six months during two years of follow-up. The questionnaire collected information on demographics, injection drug use and other substance use, sexual behavior, depressive symptoms, quality of life, and ART use. Blood specimens confirmed HIV infection at baseline and

measured CD4 cell count over follow-up. At baseline, participants responded to the questionnaire prior to receiving HIV testing results.

The exposure of interest was depressive symptoms over the past week, as assessed by the 20-item CES-D, which has been validated as a reliable measure of depressive symptoms in Vietnam (46,50). Consistent with past work, we defined severe depressive symptoms as CES-D scores ≥23, mild depressive symptoms as scores 16-22, and no symptoms as scores <16 (20,46,50,51). The transmission risk behavior outcomes were any sharing of injection equipment (needles, syringes, solutions, or distilled water) and any condomless sex, reported for the prior three months. We also descriptively examined the numbers of risk acts in the prior three months reported at each visit.

Questionnaire and laboratory data included potential confounders of the depression-risk behavior relationship. Time-fixed covariates, which were assumed to be stable throughout the study period, were marital status, age, employment status, intervention arm, history of overdose, alcohol use, HIV diagnosis prior to enrollment, and previous ART use. Employment and alcohol use could, in theory, vary over time, but these variables remained fairly constant in our population, motivating our decision to treat them as time-fixed. Time-varying covariates measured at one time point may affect subsequent depression and risk behaviors; they may also be influenced by depression and risk behaviors from a previous time point. Thus, time-varying covariates may act as either confounders or mediators, depending on the time point assessed (90,108). For this analysis, time-varying covariates were CD4 cell count category (<200, 200-499,

≥500 cells/μL), history of depressive symptoms, and history of transmission risk behaviors.

**Statistical Analysis**

In the main analysis, we used marginal structural models to estimate the average causal effect of severe depressive symptoms on the risks of any injection equipment sharing or any condomless sex (separately) in the period three to six months later, controlling for time-fixed and time-varying confounders. We evaluated each risk behavior outcome (reported with respect to the prior three-month period) at the next six-month visit in order to temporally separate it from the exposure of depressive symptoms (hereafter referred to as the "longitudinal effect"). In a second analysis, to facilitate comparison with prior research, we used marginal structural models to estimate the association between depressive symptoms and risk behaviors reported at the same visit, where temporal ordering could not be differentiated ("cross-sectional association").

We used inverse probability weighted estimation of marginal structural models (90,107). Weights were estimated from a propensity score model for the probability of severe depressive symptoms as a function of time-fixed and time-varying confounders. Time-fixed confounders had a constant (baseline) value over all visits; time-varying confounders used the value from the visit immediately preceding the visit at which depressive symptoms were assessed. In the main analysis, the propensity score model was estimated using logistic regression to model the probability of severe (vs. mild or no) depressive symptoms. In secondary analyses, we used ordinal logistic regression to separately model the three levels of depressive symptoms (severe vs. mild vs. none). Propensity score model diagnostics assessed positivity for all confounder-defined

subsets of the study population. The denominator of the weights was the predicted probability of depressive symptoms from the propensity score model, and weights were stabilized using the marginal probability of depressive symptoms in the numerator.

Application of the weights to the study population removes the association between depressive symptoms and potential confounding variables included in the propensity score model, permitting estimation of a causal effect under key assumptions (107,109) (see Discussion). In the weighted study population, we estimated RD for the risk behavior outcomes using generalized estimating equations to account for repeated observations on participants (110–112). For the longitudinal analysis, this weighted RD can be interpreted as the causal effect of depressive symptoms on the risk behavior outcome: that is, the difference in risk of the behavior in the period three to six months later if all participants had depressive symptoms compared with the risk if they all did not have depressive symptoms.

To account for missing data due to missed study visits, we used MICE (113,114), imputing and analyzing 50 datasets. We included participants who were incarcerated or died during the study period in the main analysis up until the six-month follow-up interval during which incarceration or death occurred, censoring them at that interval. In sensitivity analyses, we instead used the imputed risk behavior outcome for that six-month interval (and censored them at the following interval), given the possibility of engaging in unmeasured risk behaviors prior to incarceration or death. For all estimates, our interpretation focuses on the point estimate and confidence interval, rather than statistical significance (124). Analyses were conducted using R Version 3.4.3 (105).

## Ethics

This study was approved by the ethical review committees at the Thai Nguyen Center for Preventive Medicine, the Johns Hopkins Bloomberg School of Public Health, and the University of North Carolina at Chapel Hill Gillings School of Global Public Health. Written informed consent was obtained from all participants.

## Results

Based on inclusion criteria, all 455 participants were male, HIV-positive, and reported being sexually active and using injection drugs at baseline. The median age of participants was 35 years (interquartile range [IQR]: 30, 39), and half were married or cohabitating (47%) (Table 4.1). One-third had a high school education (34%), and the majority were employed full-time (69%). Most participants were newly diagnosed with HIV at baseline (74%), while 15% had been previously diagnosed but were not taking ART, and 11% were previously diagnosed with current ART use. The median CD4 cell count was 241 cells/μL (IQR: 126, 370). General health was rated as poor by 30%. Nearly half reported injecting heroin daily (45%), 18% had a history of overdose, and 67% reported current alcohol use. Participants completed between zero and four follow-up study visits (median=4, IQR: 2, 4) at six-month intervals over 24 months, with 87% completing at least one follow-up visit.

At baseline, 44% of participants reported severe depressive symptoms (CES-D≥23), 25% had mild symptoms (16≤CES-D≤22), and 30% had no symptoms (CES-D<16). One quarter of participants reported sex without a condom in the prior three months (24%), with a median of 10 condomless sex acts reported for those three months (IQR: 5, 20). Most participants reported sharing injection drug use equipment

with injecting partners over the past three months (73%); these participants reported a median of 21 sharing acts during those three months (IQR: 7, 52).

After the baseline visit – when the majority of participants were diagnosed with HIV and received risk reduction counseling – sharing injection equipment and condomless sex decreased across trial arms (previously reported in (45)). However, among participants attending ≥1 follow-up visits (n=397), 21% reported sharing injection equipment at ≥1 visits, and 7% reported condomless sex at ≥1 visits. The severity of depressive symptoms varied over time; among participants attending ≥1 follow-up visit, 59% experienced severe depressive symptoms at ≥1 visits (Figure 4.1). The percentage of participants experiencing competing events increased over time, with 8% incarcerated and 23% deceased at 24 months.

In our main analysis, we estimated that severe depressive symptoms (compared to no or mild symptoms) increased the risk of sharing injection equipment by 3.9 percentage points (95% CI: -1.7, 9.6) and decreased the risk of condomless sex by 1.8 percentage points (95% CI: -6.4, 2.8) in the period three to six months later (Table 4.2, Figure 4.2). In the cross-sectional analyses, the association between severe depressive symptoms and contemporaneous injection equipment sharing (RD = 6.2, 95% CI: 1.4, 11.0) was stronger than the estimated longitudinal effect, while the association with condomless sex was attenuated (RD = -0.7%, 95% CI: -4.5%, 3.0%).

In secondary analyses using three levels of depressive symptoms, there were small decreases in the risk of condomless sex as depressive symptoms increased, although all confidence intervals overlapped substantially (Table 4.2, Figure 4.3). For injection equipment sharing, patterns of risk corresponding to the three levels of

depressive symptoms differed for the longitudinal effect versus the cross-sectional association. In longitudinal analyses, we observed a U-shaped relationship in which the risk of injection equipment sharing in the period three to six months later was 12.8% (95% CI: 8.1%, 17.6%) among those with no depressive symptoms, 9.2% (95% CI: 5.3%, 13.2%) among those with mild symptoms, and 13.8% (95% CI: 9.1%, 18.5%) among those with severe symptoms. In contrast, in the cross-sectional analysis, we observed a monotonic increasing relationship in which those with no depressive symptoms had the lowest risk of 8.5% (95% CI: 5.3%, 11.8%) while those with mild symptoms had a risk of 15.5% (95% CI: 11.1%, 20.0%) and those with severe symptoms had a risk of 17.4% (95% CI: 13.1%, 21.8%).

We did not find appreciable differences in sensitivity analyses that varied censoring time for participants who were incarcerated or deceased (Figure 4.4).

**Discussion**

Using two years of longitudinal data and methods for causal inference, we found that severe depressive symptoms increased the risk of sharing injection equipment but not the risk of condomless sex among PWID. To overcome past methodological issues, we used marginal structural models to capture the episodic nature of depression, enforce temporal ordering of depression and risk behaviors, and control time-varying confounding in the analysis. By focusing on PWID living with HIV in Vietnam, a population at high risk of ongoing HIV transmission, we aimed to better understand depression as an underlying cause of risk behavior and potential onward transmission.

In our main analysis of injection equipment sharing in the period three to six months after assessment of depression, we found a RD of 3.9 (95% CI: -1.7, 9.6),

comparing participants with severe depressive symptoms to those with mild or no depressive symptoms. This longitudinal effect was only slightly weaker than the corresponding cross-sectional association (RD = 6.2, 95% CI: 1.4, 11.0) found in the analysis that did not enforce temporality. Our estimate for this effect shows that a risk difference ranging from a 1.7 percentage point decrease, a small negative association, to a 9.6 percentage point increase, a substantial positive association, is compatible with the data. Given that the overall risk of injection equipment sharing was 10% across follow-up visits, the point estimate of a 3.9 percentage point increase is substantively meaningful.

Previous research has suggested a possible non-linear relationship between the severity of depressive symptoms and occurrence of transmission risk behaviors. This literature has focused on sexual risk behavior, finding that mild depressive symptoms are associated with higher sexual risk behavior but this risk decreases with severe depressive symptoms (37). Our secondary analysis for the risk of condomless sex evaluated three levels of depressive symptoms, but findings were similar to our main analysis, suggesting slight decreases in condomless sex with increasing severity of depressive symptoms. Participants with depressive symptoms – regardless of severity – may be experiencing fatigue, social isolation, and loss of interest in sex, thereby reducing the risk of engaging in this behavior (125).

In contrast to condomless sex, we observed possible non-linearities in the secondary analysis for the risk of sharing injection equipment, which have not been observed previously. Prior studies have found an increasing risk of injecting risk behavior with increasing depressive symptom severity (39) or have not differentiated

between mild and severe symptoms (36,38,40). We found that participants with no depressive symptoms had the lowest cross-sectional risk of sharing injection equipment (suggesting a monotonic increase in risk with increasing symptom severity), while participants with mild depressive symptoms had the lowest risk of sharing injection equipment three to six months later (suggesting a U-shaped relationship, where risk increased with no symptoms or severe symptoms). Interestingly, this U-shaped relationship for longitudinal injecting risk is the inverse of previous findings on sexual risk (where those with mild depressive symptoms had the highest risk) (37). This may be due to mild depressive symptoms manifesting differently for injecting behavior compared to sexual behavior. Depressive symptoms could lead to cognitive distortions, maladaptive coping, and loss of risk aversion (126–128), and such symptoms may need to become severe in order to be expressed behaviorally as increased frequency of injection drug use (to treat severe symptoms) and consequently, greater sharing of equipment.

Although the relationship between depression and risk behaviors has been studied previously, the unique contribution of this study is its methodological rigor in inferring causality rather than correlation. Our modeling approach controlled time-varying confounding and incorporated the episodic nature of depressive symptoms by using longitudinal data from five study visits over two years. Estimation of the longitudinal effect and the cross-sectional association differed only in the timing of depressive symptoms and risk behaviors. Given that the longitudinal effect enforced temporal ordering of depressive symptoms prior to risk behaviors, we believe that it more closely reflects the causal effect. However, it is important to consider the trade-off

between temporal ordering and etiologic relevance in the context of data limitations particular to this study. Separating the measurement of depressive symptoms and risk behaviors by six months (with a three-month “blackout period” in between) was necessitated by the parent trial’s data structure. A shorter time interval with more complete data coverage may allow better capture of the effect of episodic depressive symptoms on subsequent risk behavior. In addition, this incomplete interval coverage could have attenuated effect estimates relative to what they might have been if the entire interval were included (i.e., if depressive symptoms were more likely to influence risk behaviors in the first three months of the follow-up interval).

Inferring causality relies on several key assumptions, which must be evaluated carefully in light of the limitations of this study (107,109). The assumption of no unmeasured confounding (i.e., that participants with and without depression are exchangeable) is critical to using observational studies for causal inference. Although we controlled for a variety of confounders, it is possible that unmeasured confounding biased estimates of the effect of depression on risk behaviors. We also assumed positivity (i.e., participants with and without depressive symptoms were in all confounder-defined subsets of the population) and that models were correctly specified without measurement error for covariates. Importantly, the CES-D is not diagnostic of clinical depression, and there may be measurement error if CES-D score categories do not reflect clinically relevant depressive symptoms. However, we used a conservative cut-point for severe depressive symptoms with high reliability and validity (46,50). There may also have been under-ascertainment of risk behaviors due to social desirability and recall bias. However, participants reported high levels of drug use and had been

recruited by former drug users (aware of their injection drug use), indicating a willingness to disclose sensitive behaviors. Finally, the assumption of consistency holds that any variability in treatment (i.e., multiple versions of treatment) is irrelevant to the effect of treatment on the outcome. Here, we did not model a specific treatment or intervention on depression. Therefore, our results should only be interpreted as the hypothetical effect of eliminating severe depressive symptoms without specifying the treatment or intervention used for elimination.

Our conclusions are specific to this sample and may not be representative of all PWID living with HIV. Participants were not randomly sampled and may differ from other PWID with HIV in Vietnam. While men who inject drugs drive the HIV epidemic in Vietnam, our findings may not be applicable to other groups, such as women or PWID in other regions. However, our findings may be broadly generalizable to other Asian and European countries where the HIV epidemic is concentrated among similar groups. There is also increasing relevance to understanding drivers of transmission risk behaviors among PWID in the United States, as the current opioid epidemic has begun to result in explosive HIV outbreaks (129–131). Importantly, the risk behavior outcome in our study does not allow direct prediction of forward HIV transmission risk, as we did not take into account viral suppression status, the frequency of risk acts, or partner susceptibility to HIV. These determinants of transmission will be incorporated into a future mathematical modeling analysis that will explicitly estimate forward transmission events from this study population.

We found through rigorous causal analysis that severe depressive symptoms may perpetuate the risk of sharing injection equipment among PWID living with HIV in

Vietnam. During the study period (2009-2013), there was very limited access to mental health services for people living with depression in Vietnam (88). However, in recent years, mental health services have become a national health priority, and there is growing attention and funding for increasing local services and availability of depression treatment (88,132). Screening and treating depressive symptoms among PWID presents an opportunity not only to improve mental health and drug abuse outcomes but also to reduce behaviors associated with HIV transmission risk.

**Table 4.1. Characteristics of HIV-positive male PWID in Thai Nguyen, Vietnam at baseline and follow-up visits at 6, 12, 18, and 24 months.**

| Characteristic at baseline (n = 455 participants) | Median (IQR) or N (%)[†] |
|---|---|
| Age in years (range 19-60) | 35 (30, 39) |
| Married or cohabitating | 215 (47) |
| High school education or greater | 153 (34) |
| Full-time employment | 315 (69) |
| Newly diagnosed with HIV | 336 (74) |
| Prior HIV diagnosis, no ART use | 68 (15) |
| Prior HIV diagnosis, current ART use | 51 (11) |
| CD4 cell count (cells/μl) | 241 (126, 370) |
| Self-rated health as poor | 136 (30) |
| Daily injection drug use | 207 (45) |
| History of overdose | 84 (18) |
| Current alcohol use | 307 (67) |
| Severe depressive symptoms (CES-D≥23) | 201 (44) |
| Any sharing of injection equipment in prior 3 months | 332 (73) |
| Number of sharing acts in prior 3 months (if reported any) | 21 (7, 52) |
| Any condomless sex in prior 3 months | 108 (24) |
| Number of condomless acts in prior 3 months (if reported any) | 10 (5, 20) |
| **Characteristic over follow-up (n = 397 attended ≥1 visit)** | **Median (IQR) or N (%)[‡]** |
| CD4 cell count (cells/μl) | 251 (148, 376) |
| Any severe depressive symptoms (CES-D≥23) | 235 (59) |
| Any sharing of injection equipment in prior 3 months | 82 (21) |
| Any condomless sex in prior 3 months | 29 (7) |

[†] Median and N (%) at baseline visit for all n=455 participants.

[‡] Median and N (%) across all follow-up visits for n=397 participants who attended at least one follow-up visit.

**Table 4.2. Weighted risk differences for risk behavior outcomes by depressive symptoms.**

| Injection equipment sharing: Main analysis | | | Injection equipment sharing: Secondary analysis | | |
|---|---|---|---|---|---|
| **Depressive symptoms contrast** | **Risk behavior measurement** | **RD (95% CI)** | **Depressive symptoms contrast** | **Risk behavior measurement** | **RD (95% CI)** |
| Severe vs. Not severe | Longitudinal | 3.9 (-1.7, 9.6) | Severe vs. Mild | Longitudinal | 4.6 (-1.5, 10.7) |
| | | | Severe vs. None | Longitudinal | 1.0 (-6.0, 8.0) |
| Severe vs. Not severe | Cross-sectional | 6.2 (1.4, 11.0) | Severe vs. Mild | Cross-sectional | 1.9 (-4.4, 8.2) |
| | | | Severe vs. None | Cross-sectional | 8.9 (3.6, 14.3) |
| **Condomless sex: Main analysis** | | | **Condomless sex: Secondary analysis** | | |
| **Depressive symptoms contrast** | **Risk behavior measurement** | **RD (95% CI)** | **Depressive symptoms contrast** | **Risk behavior measurement** | **RD (95% CI)** |
| Severe vs. Not severe | Longitudinal | -1.8 (-6.4, 2.8) | Severe vs. Mild | Longitudinal | -1.0 (-6.3, 4.2) |
| | | | Severe vs. None | Longitudinal | -2.6 (-8.7, 3.5) |
| Severe vs. Not severe | Cross-sectional | -0.7 (-4.5, 3.0) | Severe vs. Mild | Cross-sectional | -0.0 (-4.5, 4.4) |
| | | | Severe vs. None | Cross-sectional | -1.8 (-6.8, 3.2) |

**Figure 4.1. Distribution of depressive symptoms and competing events over 24 months.** Stacked rectangles at each time point correspond to mutually exclusive states, and shaded paths indicate transitions between states in each intervening 6-month period. The six states are severe symptoms (CES-D≥23), mild symptoms (16≤CESD≤22), no symptoms (CES-D<16), missed visit, incarceration, or death.

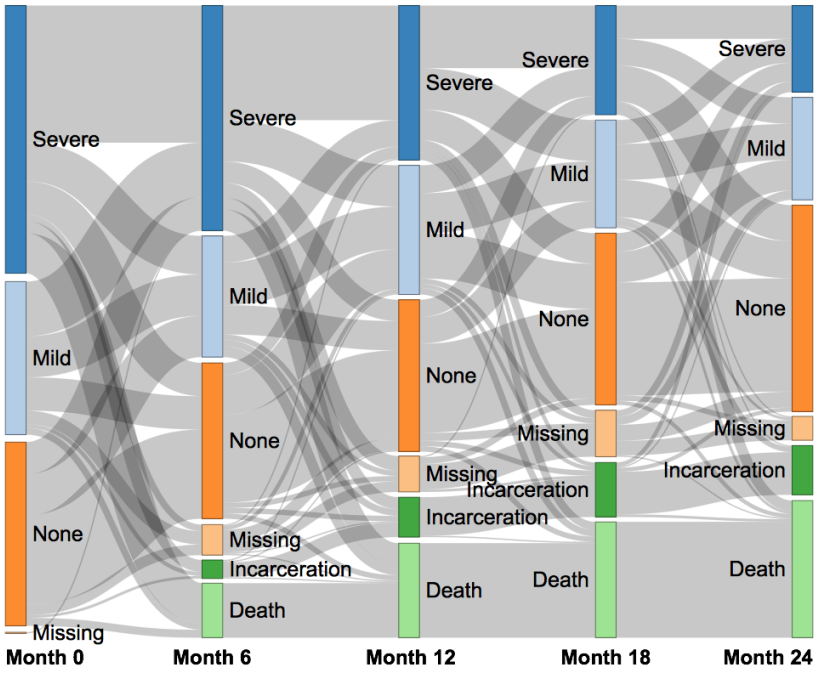


**Figure 4.2. Weighted risks of any injection equipment sharing and any condomless sex by depressive symptoms.** Severe depressive symptoms were defined as CES-D≥23; no severe symptoms were CES-D<23. We evaluated the risk behavior outcome at the next 6-month visit (longitudinal) to estimate the causal effect, and for comparison, we modeled the association at the same visit (cross-sectional).

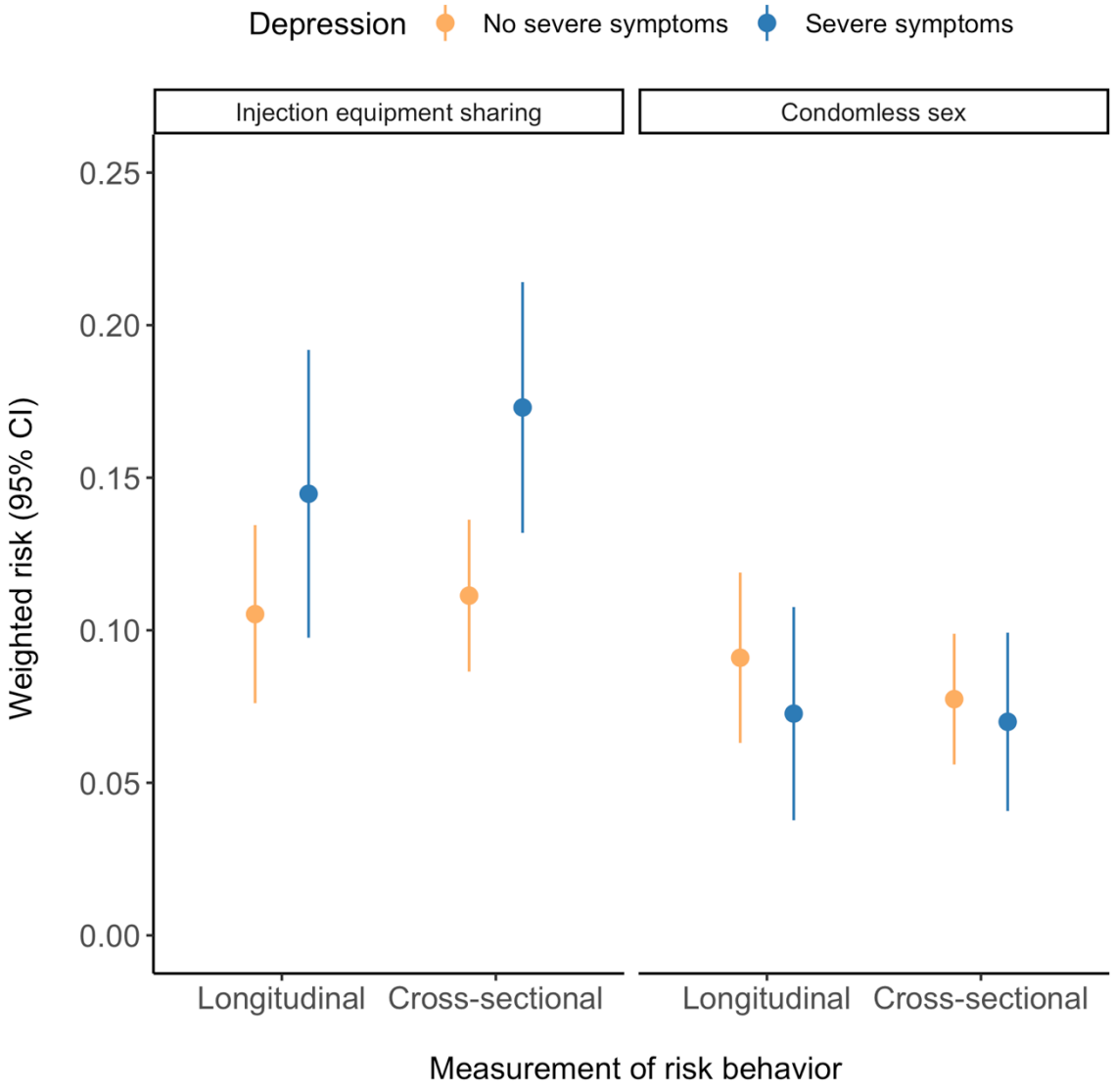


**Figure 4.3. Weighted risks of any injection equipment sharing and any condomless sex exploring three levels of depressive symptoms.** The three levels of symptoms were severe (CES-D≥23), mild (16≤CESD≤22), and none (CES-D<16). For each comparison, we evaluated the risk behavior outcome at the next 6-month visit (longitudinal) to estimate the causal effect as well as the association at the same visit (cross-sectional).

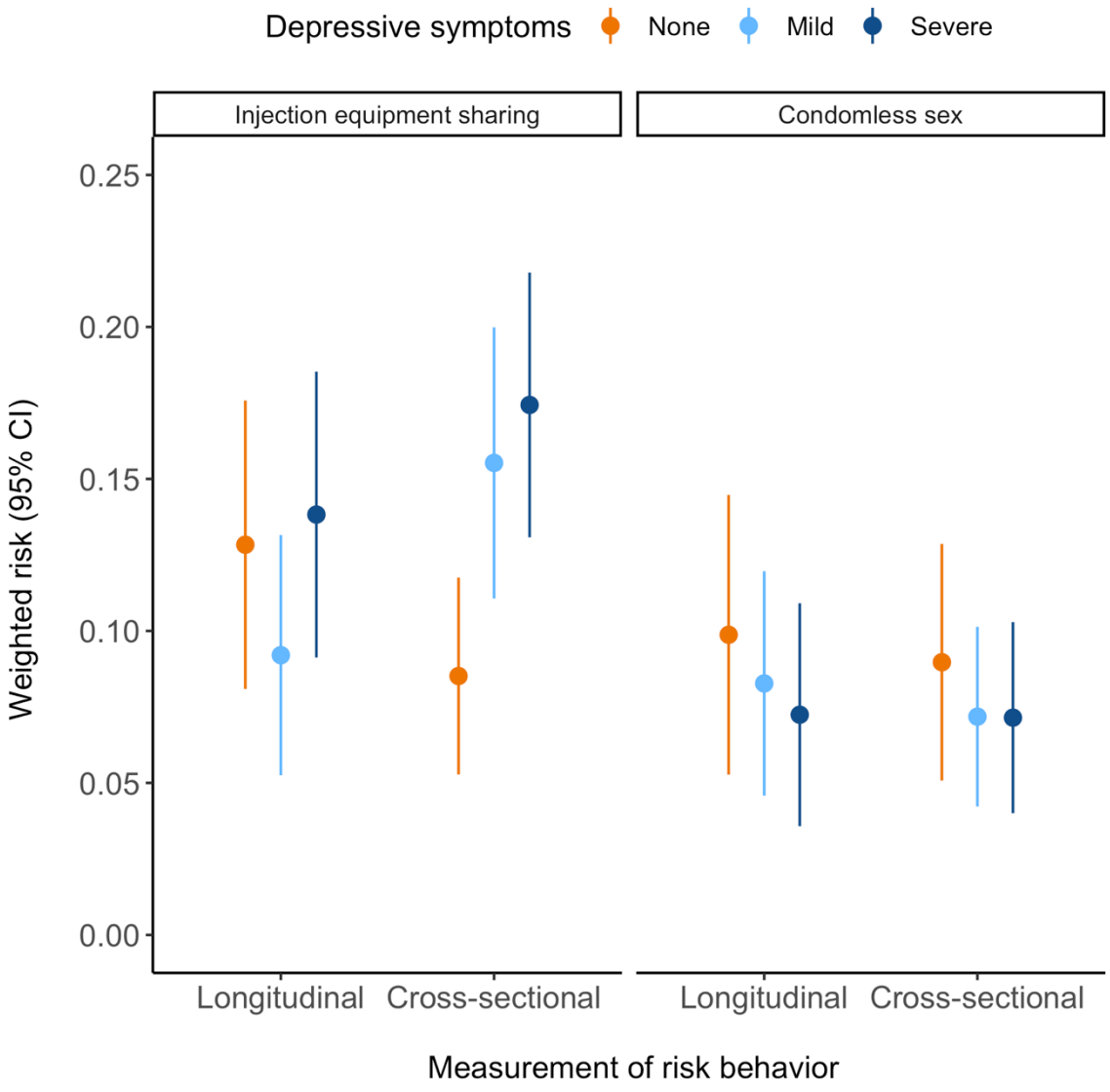
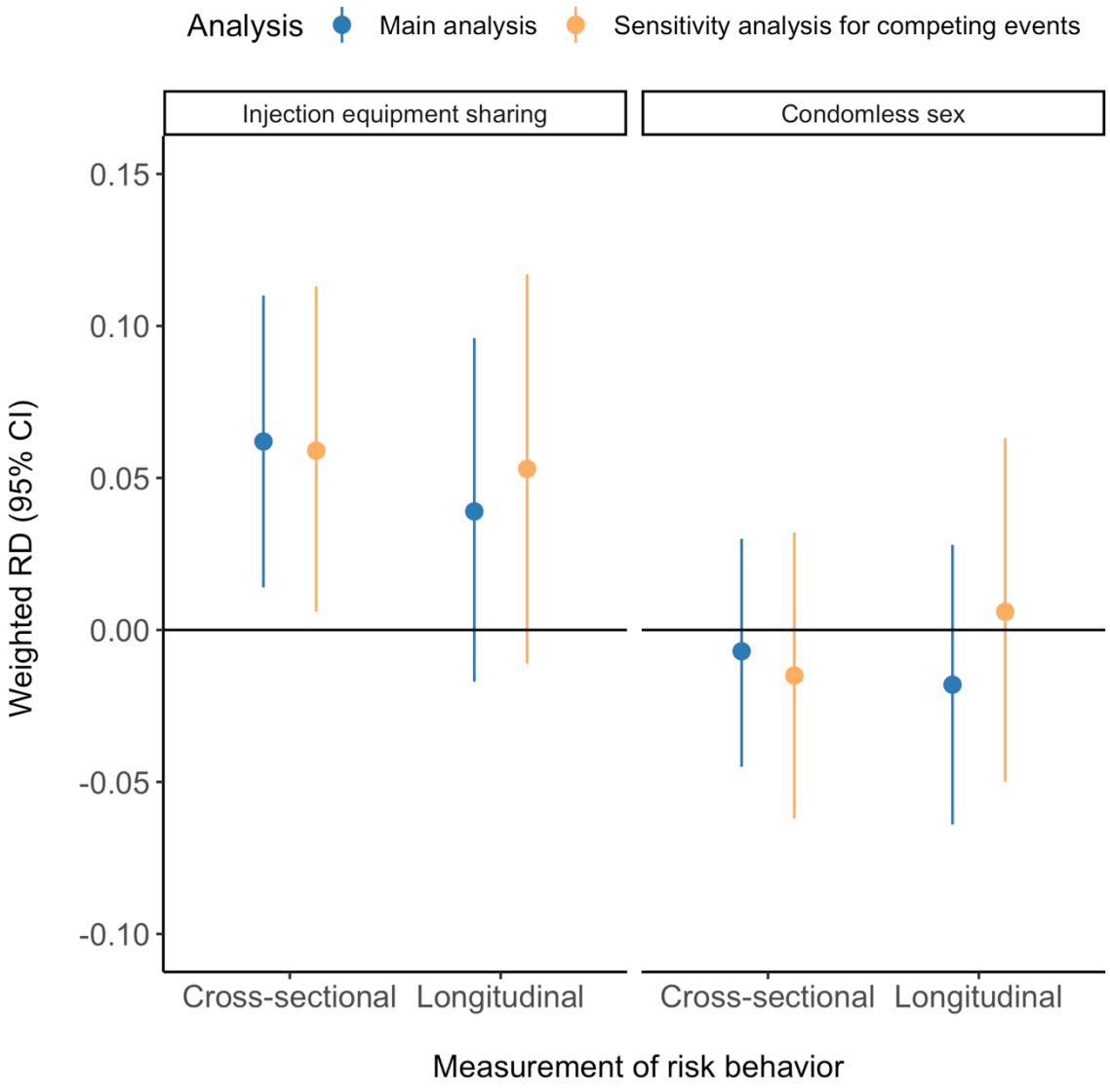


**Figure 4.4. Weighted risk differences for injection equipment sharing and condomless sex by severe depressive symptoms, based on treatment of competing events.** For participants experiencing a competing event (death or incarceration) during the study period, the main analysis included them up until the six-month follow-up interval during which the competing event occurred, censoring them at that time. The secondary analysis instead used the imputed risk behavior outcome for that six-month interval (during which time the competing event occurred) and censored them at the next six-month interval.



# CHAPTER V: DEPRESSION, ANTIRETROVIRAL THERAPY INITIATION, AND HIV VIRAL SUPPRESSION AMONG PEOPLE WHO INJECT DRUGS IN VIETNAM

## Introduction

Injection drug use is a key driver of the HIV epidemic, particularly in Asia and eastern Europe (11,12). Sharing drug preparation and injection equipment is one of the most efficient means of HIV acquisition and transmission (4,5). ART for people living with HIV can improve clinical outcomes and reduce onward transmission risk through viral suppression and a corresponding reduction in infectiousness (55). However, despite successful scale-up of HIV treatment services for PWID in some high-resource settings (133), ART use is insufficient for most PWID globally (9,10,134). In Vietnam, a setting where the HIV epidemic is concentrated among PWID (135,136), expanded ART use specifically among PWID could substantially reduce new infections (137); however, treatment is typically initiated at a late stage of infection in this population (101), hindering the impact of “treatment as prevention” on HIV transmission.

Optimizing HIV treatment as prevention among PWID may require addressing depression as an underlying cause of low treatment engagement. Up to 50% of PWID suffer from severe depressive symptoms (16–20), and though not focused on PWID, a large body of research has linked depression to poor HIV treatment outcomes (21,25–32). In recent work in Vietnam, we observed a high burden of depression among PWID living with HIV (20) and found that depression increased the risk of sharing injection drug use equipment (see Chapter IV). If depression concomitantly inhibits ART initiation

and/or viral suppression, then the corresponding increase in biological transmission risk resulting from depression could be amplified by these co-occurring injection risk behaviors.

In this study, we sought to understand the role of depression in ART initiation and viral suppression among male PWID in Vietnam. We hypothesized that severe depressive symptoms would decrease the incidence of both ART initiation and viral suppression over 6 and 12 months among PWID living with HIV. Given the disproportionate impact of both HIV and depression among PWID, it is critical to better understand depression as a potential underlying cause of poor clinical outcomes and increased transmission risk in this population.

## Methods

### Parent Trial Design and Population

This study was nested within a randomized controlled trial of a multi-level HIV stigma and risk reduction intervention that enrolled PWID living with HIV in Thai Nguyen, Vietnam from 2009 to 2013 (45). Thai Nguyen is a province in northeastern Vietnam with an estimated HIV prevalence of 34% among its approximately 6,000 PWID (57–59). Participants were recruited via snowball sampling from the 32 sub-districts of Thai Nguyen with the most PWID. The trial enrolled 455 participants who met the following eligibility criteria: 1) HIV-positive (confirmed through study testing), 2) male (because 97% of PWID in Thai Nguyen are male, and females would require a different intervention), 3) age ≥18 years, 4) reported having sex and injecting drugs in the prior six months, and 5) planned to live in Thai Nguyen for the next 24 months. As part of HIV testing and counseling at trial baseline, participants were referred to ART clinics. In

2009, national eligibility criteria for ART were CD4 cell count ≤200 cells/$\mu$l and had moved to CD4 cell count ≤350 cells/$\mu$l by 2013 (101,102).

In a two-stage process, the 32 sub-districts where participants lived were randomized to a structural intervention, and the 455 enrolled participants across sub-districts were randomized to an individual-level intervention (45). This process resulted in four trial arms to which participants could belong: 1) control (standard of care), 2) individual (individual-level intervention only), 3) sub-district (sub-district-level structural intervention only), and 4) combined (structural and individual interventions). The structural intervention aimed to reduce community-level HIV and injection drug use stigma, and the individual intervention provided support to participants in coping with HIV and reducing transmission risk behaviors. As previously reported (45), no differences in transmission risk behaviors were observed across trial arms.

**Measures**

Questionnaire and laboratory data were collected at study visits every six months during the two-year trial (baseline, 6, 12, 18, 24 months). The questionnaire was administered in a face-to-face interview and collected information on demographics, general health, injection drug use and other substance use, depressive symptoms, HIV transmission risk behaviors, history of HIV testing, and ART use. Blood specimens were collected to confirm HIV infection at baseline and to measure CD4 cell count at all visits. Participants responded to the baseline questionnaire prior to receiving HIV testing results. As part of the questionnaire at each visit, participants were asked if they were currently taking ART, and in addition, participants were seen by the study physician who also ascertained current ART use.

The exposure of interest was severe depressive symptoms over the past week, as assessed with the 20-item CES-D, which has been validated as a reliable measure of depressive symptoms in Vietnam (46,50). Consistent with past work including studies in Vietnam (20,46,50,51), we defined severe depressive symptoms as CES-D scores ≥23 and no or mild symptoms as scores <23.

We specified two outcomes of interest: ART initiation and viral suppression. A participant was considered to have initiated ART in the prior six months as of the first visit at which the study physician reported participant ART use. If the physician's report of ART use was missing (occurring for 17% of all study visits), we used the participant's self-report of ART use in the previous six months. In prior work in this population, we found 92% concordance between self- and physician-reported ART use (103). Because viral load was not measured in the parent trial, for the viral suppression analyses we performed HIV RNA testing on stored blood plasma specimens using COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test platform (Roche Diagnostics GmbH) with a lower limit of detection of 20 copies/mL. Participants were considered to have experienced the viral suppression outcome as of the first visit with viral load <400 copies/mL. Missing viral load data resulted from insufficient sample volume (<1mL) for some of the stored specimens at follow-up visits: 31% at 6 months, 59% at 12 months, 48% at 18 months, and 55% at 24 months. To limit the influence of missing data in this analysis, we evaluated both outcomes of interest only at the two earliest follow-up visits (6 and 12 months).

We identified potential confounders *a priori* as questionnaire or laboratory variables that could plausibly affect depression, ART initiation, and viral suppression.

These hypothesized confounders included marital status, age, employment status, intervention arm, CD4 cell count, self-rated general health, recent alcohol use, history of overdose, frequency of injection drug use, recent sharing of injection equipment, and recent condomless sex. To prevent inclusion of variables mediating the relationship between depression and a given outcome, all potential confounder values corresponded to the time period prior to exposure assessment (90,108).

Study outreach workers attempted to trace participants who missed a visit using the contact information collected at baseline. During tracing procedures, outreach workers asked participant contacts if the participant had died or was incarcerated. We therefore considered death and incarceration to have been ascertained at all visits, allowing us to treat them as competing events for the outcomes of interest.

**Statistical Analysis**

We used a semi-parametric inverse probability-weighted estimator of the cumulative incidence of ART initiation and viral suppression (analyzed separately), accounting for the time-varying nature of depression and confounders and the occurrence of the competing events of death and incarceration (138,139). Participants who did not experience an event were administratively censored at the end of follow-up; no other censoring occurred. To estimate the effect of depression on the 6- and 12-month cumulative incidence of ART initiation and viral suppression, we first estimated the cumulative incidence of each outcome at each time point in three scenarios: 1) Natural course: the incidence of the outcome in the observed study population, 2) Never depressed: the incidence of the outcome if participants never had severe depressive symptoms (i.e., symptoms were mild or absent, defined as CES-D score <23, at all

study visits up to and including the visit prior to outcome ascertainment), and 3) Always depressed: the incidence of the outcome if participants always had severe depressive symptoms (CES-D ≥23 at all study visits up to and including the visit prior to outcome ascertainment). Given that depressive symptoms vary over time, these two extreme conditions were intended to capture the largest possible difference: the risk of the outcome if participants always had severe symptoms vs. the risk of the outcome if participants never had severe symptoms.

In the natural course (scenario 1), the cumulative incidence of each outcome $Y$ (ART initiation, viral suppression) was estimated as the number of participants who experienced the outcome of interest $(J = 1)$, rather than a competing event $(J = 2)$, by the 6- and 12-month follow-up visits ($t = 6,\ t = 12$ months), divided by the total sample size $n$:

$$\hat{P}(Y \leq\ t, J = 1)\ = \frac{1}{n}\sum_{i=1}^{n} I(Y_i \leq t,\ J_i = 1) \quad (1)$$

In the never-depressed scenario (scenario 2), we estimated the cumulative incidence of the outcome using data only from participants who were never depressed $(\pi = 1)$ and applied inverse probability weights $\frac{1}{\hat{P}(\pi = 1|W_i)}$ such that they represented the full study population based on hypothesized confounders $W$:

$$\hat{P}(Y \leq\ t, J = 1)\ = \frac{1}{n}\sum_{i=1}^{n} \frac{\pi_i\, I(Y_i \leq t, J_i = 1)}{\hat{P}(\pi = 1|W_i)} \quad (2)$$

In the always-depressed scenario (scenario 3), we estimated the cumulative incidence of the outcome using data only from participants who were always depressed $(\Delta = 1)$ and applied inverse probability weights $\frac{1}{\hat{P}(\Delta = 1)|W_i}$ such that they represented the full study population based on hypothesized confounders $W$:

$$\hat{P}(Y \leq t, J = 1) = \frac{1}{n}\sum_{i=1}^{n} \frac{\Delta_i I(Y_i \leq t, J_i = 1)}{\hat{P}(\Delta = 1 | W_i)} \quad (3)$$

For the never-depressed scenario, the weights were estimated from a logistic regression model for the probability of no severe depressive symptoms, conditional on having no severe symptoms at prior visits (i.e., the model was estimated using the full population at baseline, and over follow-up, participants were censored from the model after the visit at which severe symptoms were ascertained). For the always-depressed scenario, the weights were estimated from a logistic regression model for the probability of severe depressive symptoms, conditional on having severe symptoms at prior visits (similarly, the model was estimated using the full population at baseline, and over follow-up, participants were censored from the model after the visit at which they no longer had severe symptoms). Both probabilities were modeled as a function of follow-up time (in months), intervention arm (control, individual, sub-district, combined), time-varying CD4 cell count category (<200, 200-349, 350-499, ≥500 cells/μL), and baseline values of marital status (single, married or cohabitating, separated, divorced or widowed), age (in years), employment status (full-time, part-time, unemployed), self-rated general health (good, fair, poor), alcohol use (any/none), history of overdose (any/none), frequency of injection drug use (number of days injected in last 90 days), sharing of injection equipment (any/none in last 90 days), and condomless sex (any/none in last 90 days). Although several of the variables we treated as time-fixed (e.g., employment status, alcohol use) could, in theory, vary over time, they remained fairly constant in our population, motivating our decision to include only baseline values.

Each participant's weight at a given time point was calculated as the reciprocal of the cumulative product of the model-predicted probabilities for their observed

depression status (i.e., never-depressed or always-depressed). We evaluated the distribution of probabilities to assess positivity for all confounder-defined subsets of the study population and ensure balance of covariates in the weighted sample. Across all analyses, there were no extreme weight values (range between 1 and 20).

Application of the weights to the study population removes the association between the potential confounding variables included in the model and depressive symptoms, permitting estimation of a causal effect between depression and our outcomes of interest under key assumptions of consistency, conditional exchangeability, positivity, and no measurement error (107,109) (see Discussion). In the weighted study population, we estimated the cumulative incidence of each outcome at 6 and 12 months as the cumulative sum of the weights for participants experiencing the outcome, divided by the total sample size. To ensure that depression occurred prior to the outcome, outcomes lagged their assigned weight values by 6 months (i.e., baseline weight values were used for outcomes at 6 months; 6-month weight values were used for outcomes at 12 months). We estimated the CID contrasting the never-depressed and always-depressed scenarios: that is, the difference in 6- and 12-month cumulative incidence of the outcome (ART initiation, viral suppression) if participants always had severe depressive symptoms, compared with the risk if participants never had severe depressive symptoms. For cumulative incidence and CID estimates, we used a conservative influence function-based estimator of the variance. This estimator was implemented by taking the variance of the differences between the cumulative incidence estimate and each observation’s weighted contribution.

In our main analyses, the cumulative incidence of each outcome was estimated for participants who had not experienced that outcome at baseline, resulting in slightly different analytic samples for the two outcomes (e.g., participants who reported ART at baseline, but were not virally suppressed, were included in the viral suppression analysis, but not in the ART initiation analysis). In a second set of analyses, we restricted analysis of both outcomes to the same sample (participants with neither ART use nor viral suppression at baseline) to facilitate more direct comparison of estimates across outcomes.

There was substantial missing data due to insufficient sample volume for measuring viral load (31% at 6 months, 59% at 12 months) in addition to intermittent missing data on other study variables not due to death or incarceration (<15% across all variables at all visits). To address missing data, we used MICE (113,114), analyzing 50 complete datasets with values imputed for depression, ART initiation, viral suppression, and all hypothesized confounders. We used Rubin's formula to pool results from the 50 imputed datasets and calculate variance accounting for within- and between-imputation variability (113).

For all estimates, we focused interpretation on the point estimate and confidence interval, rather than statistical significance (124). Analyses were conducted using R Version 3.4.3 (105).

**Ethics**

The parent trial and this analysis were approved by the ethical review committees at the Thai Nguyen Center for Preventive Medicine, the Johns Hopkins Bloomberg School of Public Health, and the University of North Carolina at Chapel Hill

Gillings School of Global Public Health. Written informed consent was obtained from all participants.

**Results**

Among the 455 participants at baseline, the median age was 35 years (IQR: 30, 39), nearly half (47%) were married or cohabitating, and most (69%) were employed full-time. Most participants (73%) reported sharing injection drug use equipment with injecting partners over the past three months, and one-quarter (24%) reported sex without a condom in the prior three months. Prior to HIV testing at baseline, 74% of participants reported no previous HIV diagnosis. Table 5.1 shows additional characteristics of the study population.

The percentage of participants with severe depressive symptoms (CES-D ≥23) was 44% at baseline, decreasing to 37% at 6 months and 25% at 12 months (Table 5.1). This decreasing prevalence of depression over time was likely due in part to disproportionately higher risks of competing events over follow-up among participants who had severe depressive symptoms at baseline (Table 5.2, Figure 5.2). At baseline, only 13% of participants reported current ART use; this percentage increased to 33% and 36%, at 6 and 12 months, respectively. There was a slight increase in CD4 cell count from baseline (median 241 cells/μL) to 6 months (median 251 cells/μL) and 12 months (260 cells/μL). The median HIV viral load was 4.3 $\log_{10}$ copies/mL at baseline, decreasing to 3.6 $\log_{10}$ copies/mL at 6 months, and then increasing to 3.9 $\log_{10}$ copies/mL at 12 months.

Among 397 participants who had not initiated ART at baseline, the cumulative incidence of ART initiation in the natural course scenario (unweighted study population)

was 24% (95% CI: 20%, 29%) at 6 months and 35% (95% CI: 30%, 40%) at 12 months (Table 5.3, Figure 5.1). In the never-depressed scenario (weighted incidence if participants never had severe depressive symptoms), the cumulative incidence of ART initiation was slightly higher: 27% (95% CI: 20%, 34%) at 6 months and 37% (95% CI: 30%, 44%) at 12 months. In the always-depressed scenario (weighted risk of outcome if participants always had severe depressive symptoms), the cumulative incidence of ART initiation was somewhat lower: 20% (95% CI: 13%, 27%) at 6 months and 30% (95% CI: 22%, 38%) at 12 months.

Among 342 participants who were not virally suppressed at baseline (HIV RNA ≥400 copies/mL), the cumulative incidence of viral suppression in the natural course was 20% (95% CI: 14%, 25%) at 6 months and 44% (95% CI: 34%, 54%) at 12 months (Table 5.3, Figure 5.1). Estimates of cumulative incidence were similar in both of the hypothetical depression scenarios. In the never-depressed scenario, the cumulative incidence of viral suppression was 19% (95% CI: 11%, 27%) at 6 months and 46% (95% CI: 31%, 62%) at 12 months. In the always-depressed scenario, the cumulative incidence of viral suppression was 20% (95% CI: 11%, 28%) at 6 months and 48% (95% CI: 29%, 68%) at 12 months.

Severe depressive symptoms (compared with no severe symptoms) decreased the cumulative incidence of ART initiation, with CID values comparing always vs. never having severe depressive symptoms of -7.5 (95% CI: -17.2, 2.2) percentage points at 6 months and -7.1 (95% CI: -17.9, 3.7,) percentage points at 12 months (Figure 5.3). There were no appreciable differences in the cumulative incidence of viral suppression

at 6 months (CID = 0.3 percentage points, 95% CI: -11.3, 11.9) or 12 months (CID = 2.0 percentage points, 95% CI: -21.8, 25.8).

Findings were largely unchanged in analyses where we estimated both outcomes in the set of participants who had not experienced either outcome at baseline (Figure 5.4).

**Discussion**

Using longitudinal data on PWID living with HIV in Vietnam, we found that severe depressive symptoms decreased the cumulative incidence of ART initiation, but not viral suppression, over one year. We used a rigorous methodological approach that addressed the episodic nature of depression, time-varying confounding, substantial missing data, and common competing events of death and incarceration. By focusing on a population disproportionately impacted by both depression and HIV, we sought to better understand depression as a cause of phenomena that could lead to poor health outcomes and potential onward transmission. Although an inverse relationship between depression and HIV treatment-related outcomes has been established, prior work has largely focused on HIV patients who were engaged in clinical care (21,25–31). As the majority of our study population was newly diagnosed and/or not receiving ART at the start of follow-up, this analysis provides insights into the association between depression and HIV treatment-related outcomes outside of well-established clinical cohorts.

We contrasted two extreme conditions intended to capture the largest possible difference by depression: the risk of the outcome if participants always had severe symptoms vs. the risk of the outcome if participants never had severe symptoms. For

the ART initiation outcome, the CID for the always- vs. never-depressed scenarios was approximately -7 percentage points at both 6 and 12 months. These effect estimates relied on small sample sizes (i.e., the subsets of participants who stayed depressed or were never depressed, respectively), resulting in wide confidence intervals; that is, a CID ranging from a large decrease in ART initiation (-17 to -18 percentage points) to a slight increase in ART incidence (2 to 4 percentage points) is compatible with the data. Given that the cumulative incidence of ART initiation in the observed study population (natural course) was 24% at 6 months and 35% at 12 months, the 7-percentage-point decrease in cumulative incidence represented by the point estimate is substantively meaningful. Despite this relationship between depression and ART initiation, we did not observe an effect of depression on viral suppression: the CIDs at 6 and 12 months were both near-zero with extremely wide confidence intervals.

Our seemingly disparate findings for the ART initiation and viral suppression outcomes should be interpreted in light of potential measurement error. We observed discrepancies between measurements of ART use and viral load across all study visits. Higher-than-expected numbers of participants did not report ART use but had very low or undetectable viral load (e.g., 14% of the study population did not report any ART use at study baseline, but had viral loads <400 copies/mL). As a result, the estimated incidence of viral suppression exceeded that of ART initiation at 12 months, even when assessment of both outcomes was restricted to the same set of participants with neither ART use nor viral suppression at baseline. Similar discrepancies between reported ART use and viral load measurements have been observed in previous research and have been considered to result from a combination of elite suppressors and ART reporting

bias (140–142). Given that elite suppression is rare (143), we assume that discrepancies between ART use and viral load in our study more commonly resulted from ART reporting bias. Of particular relevance, in a similar population of PWID living with HIV in Vietnam (enrolled in HIV Prevention Trials Network [HPTN] 074), 13% of participants who reported no prior ART had antiretroviral drugs detected through study screening (142). Although no antiretroviral screening could be performed in our study, we used the physician-reported ART variable (in addition to participant reports) to reduce possible reporting bias. However, the reporting physician only saw participants as part of the study and may have been unaware of ART use overseen by external providers if not disclosed by the participant.

In addition to the possibility of elite suppressors and under-reported ART use, apparent discrepancies in our study findings may also result from uncertainty in the viral suppression outcome. There was substantial missing data on viral load due to insufficient volume of many collected samples. Because missingness was thought to occur at random and did not appear to be linked to depression or other participant characteristics, we used multiple imputation to impute viral suppression outcomes for the 31% and 59% of participants with missing data at 6 and 12 months, respectively. There was considerable variability across imputations, resulting in imprecise estimates of cumulative viral suppression incidence and corresponding risk differences. Compared to cumulative incidence estimates for the ART initiation outcome across imputed datasets (Figure 5.5), estimates for the viral suppression outcome showed greater variability, particularly at 12 months (Figure 5.6), with this source of uncertainty resulting in the wider CID confidence intervals for this outcome vs. the ART outcome (Figure 5.8

vs. 5.7). As such, while there may be biological or behavioral mechanisms through which depression decreases ART initiation but not viral suppression, we cannot rule out missing data and measurement error as factors contributing to this apparently paradoxical finding in our study.

Other study limitations were possible violations of the assumptions (107,109) required for valid interpretation of our CIDs as representing causal effects. First of these assumptions is sequential conditional exchangeability, which in our case holds that participants who never have depression and who always have depression are exchangeable, conditional on measured confounders. We controlled for a variety of confounders through the use of inverse probability weights, but it is possible that unmeasured confounders led to imbalances in depression groups, thereby biasing estimates of the effect of depression on our outcomes. The second assumption is positivity, which requires that there were participants who were never depressed and who were always depressed in all confounder-defined subsets of the study population. We used model diagnostics to verify this assumption. Finally, the assumption of consistency, or treatment version irrelevance, holds that any variability in treatment (i.e., multiple versions of treatment) is irrelevant to the effect of treatment on the outcome. Here, we did not model a specific treatment or intervention on depression, and our results should only be interpreted as the hypothetical effect of eliminating severe depressive symptoms, without specifying the precise treatment or intervention used for elimination. Further research on the high burden of depression in PWID and the potentially overlapping experiences of stigma and other mental illness in this population could inform the design of future intervention.

Our findings are specific to this study sample, which may not be representative of all PWID living with HIV. Although snowball sampling enabled the study team to access a hard-to-reach population, the non-random nature of our study sample potentially limits generalizability of findings to PWID with HIV in Vietnam who were not recruited. In addition, while men who inject drugs are a key population in the Vietnamese HIV epidemic in Vietnam, our findings may not be applicable to women who inject drugs, a key population for HIV prevention efforts in other parts of the world (144).

In conclusion, we found that severe depressive symptoms may have hindered ART initiation but not viral suppression among PWID living with HIV in Vietnam. During the study period (2009-2013), there were extremely limited treatment services for depression in Vietnam, but in recent years, mental health services have received growing prioritization and funding (88,132). Screening and treating depressive symptoms among PWID present opportunities not only to improve mental health and drug abuse outcomes, but also to increase uptake of lifesaving HIV treatment. Future work probing the seemingly antagonistic effect of depression on treatment uptake – but not viral suppression – may help to elucidate the relationships between these two outcomes and inform the design of interventions promoting HIV care engagement, treatment initiation, and viral suppression among PWID.

**Table 5.1. Time-fixed and time-varying characteristics of 455 HIV-positive male PWID in Thai Nguyen, Vietnam at study baseline, 6 months, and 12 months.**

| Time-fixed characteristics | Baseline Median (IQR) or N (%) | | |
|---|---|---|---|
| Age in years (range 19-60) | 35 (30, 39) | | |
| Married or cohabitating | 215 (47) | | |
| Full-time employment | 315 (69) | | |
| Number of days (in past 90 days) injected heroin | 70 (15, 90) | | |
| Any sharing of injection equipment (past 90 days) | 332 (73) | | |
| Any sex without a condom (past 90 days) | 108 (24) | | |
| Self-rated health as poor | 136 (30) | | |
| History of overdose | 84 (18) | | |
| Any alcohol use | 307 (67) | | |
| No prior HIV diagnosis | 336 (74) | | |
| **Time-varying characteristics** | **Baseline Median (IQR) or N (%)** | **6 Months Median (IQR) or N (%)[i]** | **12 Months Median (IQR) or N (%)[ii]** |
| Severe depressive symptoms (CES-D≥23)[iii] | 201 (44) | 169 (37) | 116 (25) |
| ART use[iv] | 58 (13) | 148 (33) | 165 (36) |
| CD4 cell count (cells/μl)[v] | 241 (126, 370) | 251 (154, 387) | 260 (151, 382) |
| HIV viral load (log10 copies/mL)[vi] | 4.3 (2.6, 4.9) | 3.6 (1.8, 4.5) | 3.9 (3.2, 4.5) |

[i] Percentages are based on the total sample size of 455 participants. By 6 months, 55 (12%) participants had experienced competing events of death or incarceration.

[ii] Percentages are based on the total sample size of 455 participants. By 12 months, 101 (22%) participants had experienced competing events of death or incarceration.

[iii] There was missing data on CES-D scores (not due to death or incarceration) for 1 participant at baseline, 23 participants at 6 months, and 27 participants at 12 months.

[iv] There was missing data on ART use (not due to death or incarceration) for 6 participants at baseline, 23 participants at 6 months, and 27 participants at 12 months.

[v] There was missing data on CD4 cell count (not due to death or incarceration) for 9 participants at baseline, 43 participants at 6 months, and 50 participants at 12 months.

[vi] HIV viral load was fully observed at baseline, but missing data (not due to death or incarceration) occurred for 162 participants at 6 months and 295 participants at 12 months.

**Table 5.2. Distribution of depression, competing events, and missing data over 12 months, by baseline depression.**

| | Severe depressive symptoms, N = 201 n (%)[i] | No severe symptoms, N = 253 n (%)[i] |
|---|---|---|
| **Severe depressive symptoms** | | |
| At 6 months | 103 (51%) | 65 (26%) |
| At 12 months | 73 (36%) | 43 (17%) |
| **Incarceration** | | |
| At 6 months | 9 (4%) | 5 (2%) |
| At 12 months | 18 (9%) | 11 (4%) |
| **Death** | | |
| During 0-6 months | 30 (15%) | 11 (4%) |
| During 6-12 months | 14 (7%) | 16 (6%) |
| **Missing data[ii] on ART** | | |
| At 6 months | 5 (2%) | 18 (7%) |
| At 12 months | 11 (5%) | 16 (6%) |
| **Missing data[ii] on viral load** | | |
| At 6 months | 70 (35%) | 91 (36%) |
| At 12 months | 119 (59%) | 176 (70%) |

[i] Percentages are based on the sample sizes of 201 participants with severe depressive symptoms at baseline and 253 participants with no or mild depressive symptoms at baseline. One participant had a missing CES-D score at baseline.
ii Frequencies and percentages correspond to participants who were missing data not due to death or incarceration.

**Table 5.3. Estimates of 6-month and 12-month cumulative incidence of ART initiation and viral suppression by depression scenario and cumulative incidence differences contrasting always-depressed vs. never-depressed scenarios.** Cumulative incidence estimates for the natural course (observed study population) are provided for reference. The study sample for the ART initiation outcome was n=397 participants without ART use at baseline, and the study sample for the viral suppression outcome was n=342 participants without viral suppression at baseline.

| | 6-month cumulative incidence (95 CI%) | 6-month CID by depression (95% CI) | 12-month cumulative incidence (95 CI%) | 12-month CID by depression (95% CI) |
|---|---|---|---|---|
| **ART Initiation** | | | | |
| Always Depressed | 0.20 (0.13, 0.27) | -0.08 (-0.17, 0.02) | 0.30 (0.22, 0.38) | -0.07 (-0.18, 0.04) |
| Natural Course | 0.24 (0.20, 0.29) | | 0.35 (0.30, 0.40) | |
| Never Depressed | 0.27 (0.20, 0.34) | | 0.37 (0.30, 0.44) | |
| **Viral Suppression** | | | | |
| Always Depressed | 0.20 (0.11, 0.28) | 0.00 (-0.11, 0.12) | 0.48 (0.29, 0.68) | 0.02 (-0.22, 0.26) |
| Natural Course | 0.20 (0.14, 0.25) | | 0.44 (0.34, 0.54) | |
| Never Depressed | 0.19 (0.11, 0.27) | | 0.46 (0.31, 0.62) | |

**Figure 5.1. Estimates of 6-month and 12-month cumulative incidence of ART initiation and viral suppression.** The study sample for the ART initiation outcome was n=397 participants without ART use at baseline, and the study sample for the viral suppression outcome was n=342 participants without viral suppression at baseline.

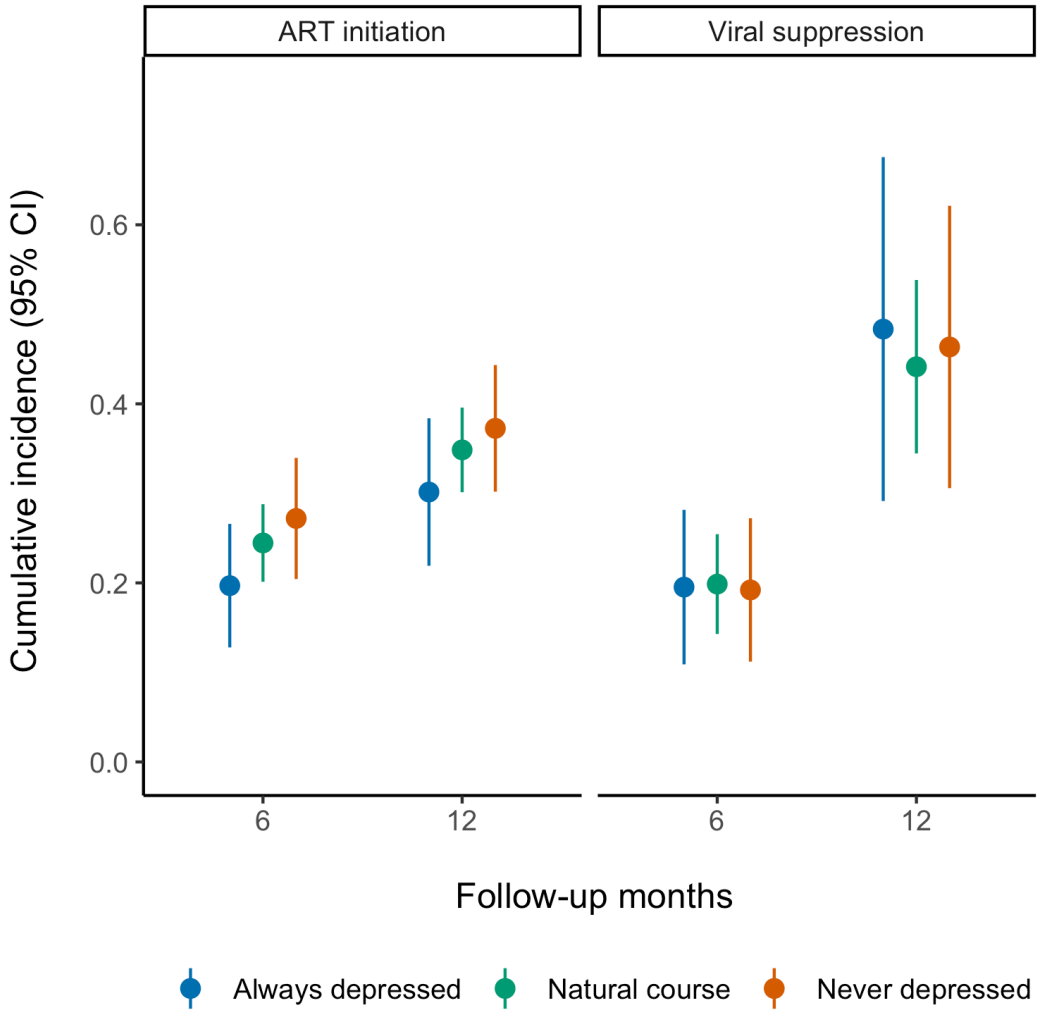


**Figure 5.2. Weighted cumulative incidence of competing events (death, incarceration) prior to ART initiation (n = 397) and viral suppression (n = 342).**

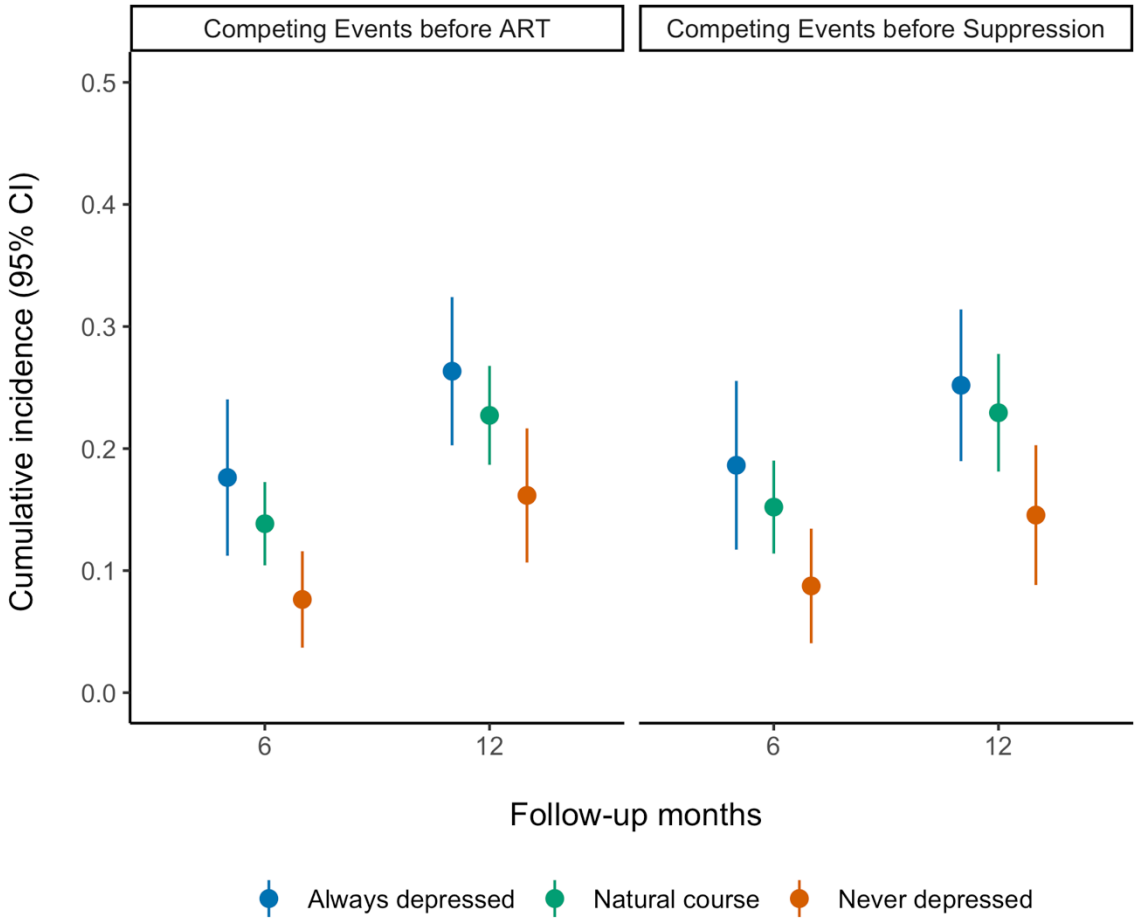


**Figure 5.3. Estimates of 6-month and 12-month cumulative incidence differences for ART initiation and viral suppression, contrasting always-depressed vs. never-depressed scenario.** The study sample for the ART initiation outcome was n=397 participants without ART use at baseline, and the study sample for the viral suppression outcome was n=342 participants without viral suppression at baseline.

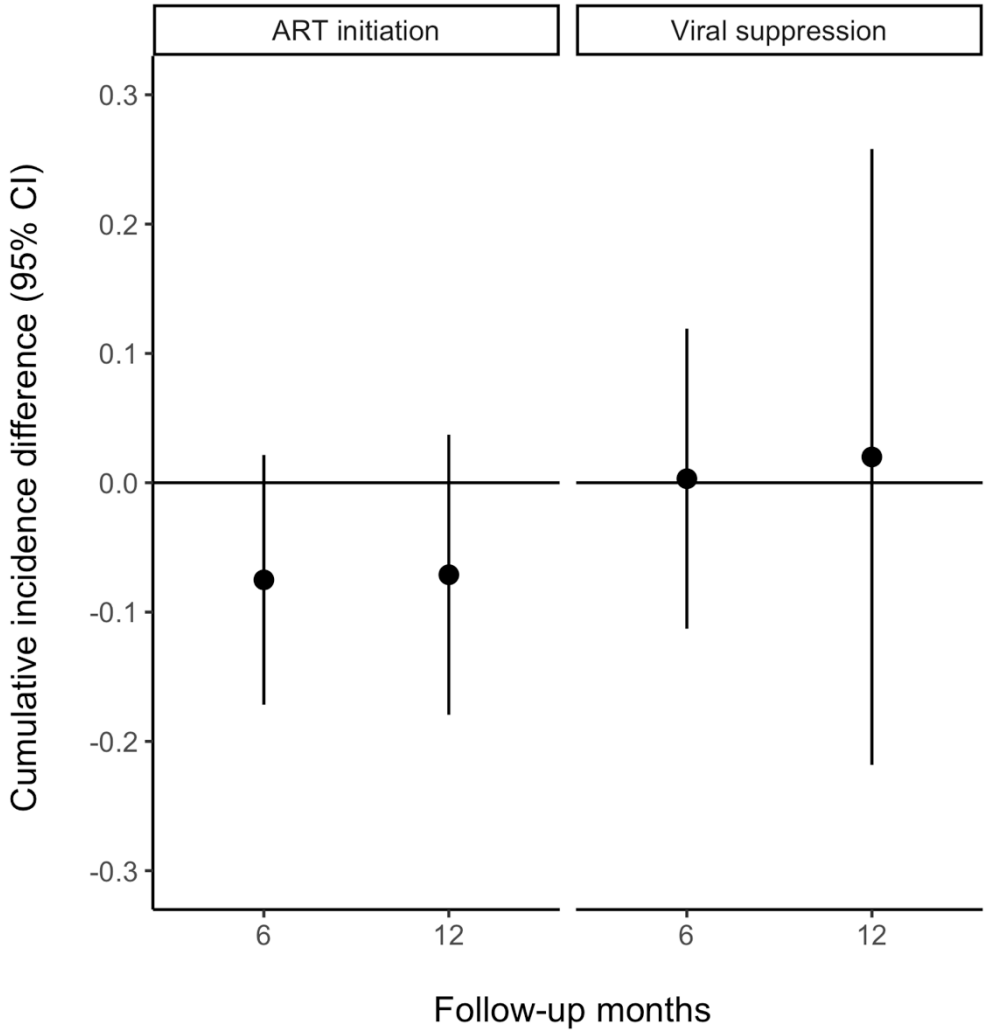


**Figure 5.4. Weighted cumulative incidence of ART initiation and viral suppression in the same sample of participants with neither ART initiation nor viral suppression at baseline (n = 332).**

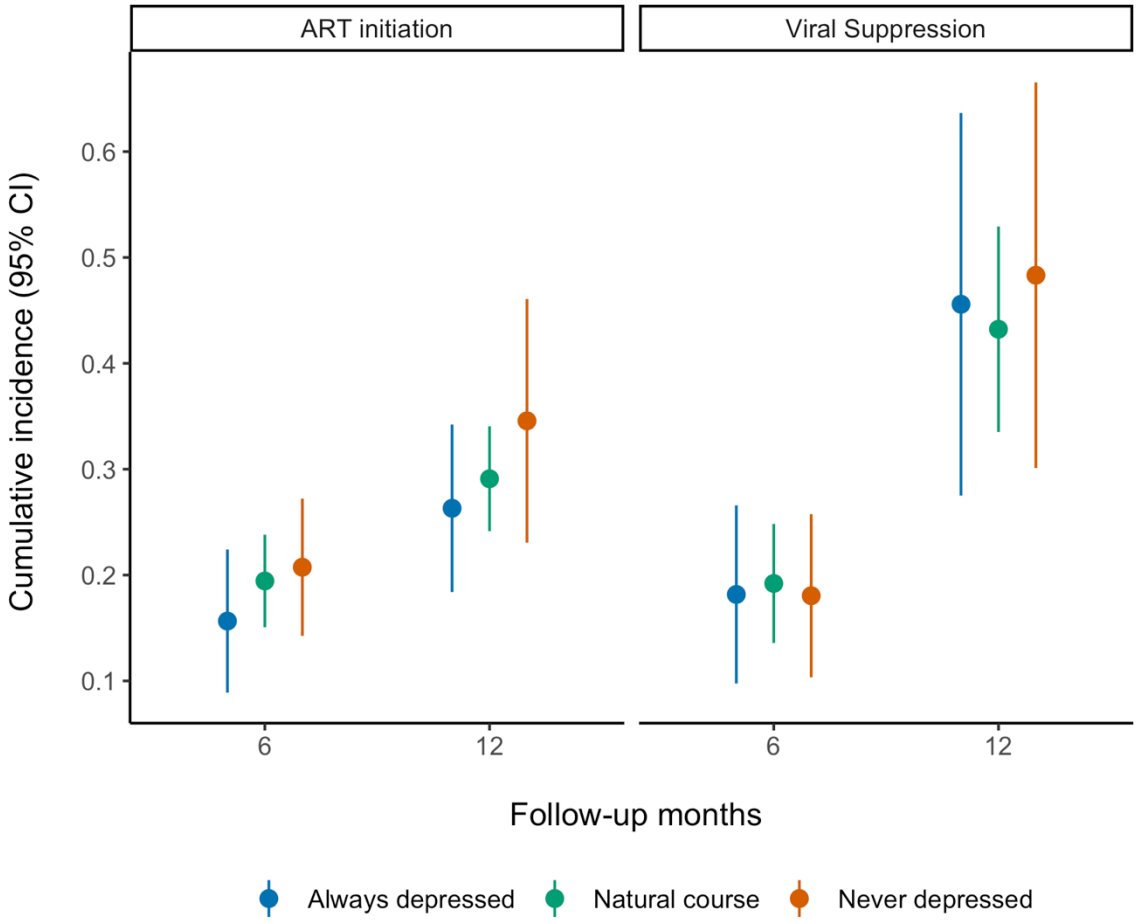


**Figure 5.5. Cumulative incidence of ART initiation, by imputation.**

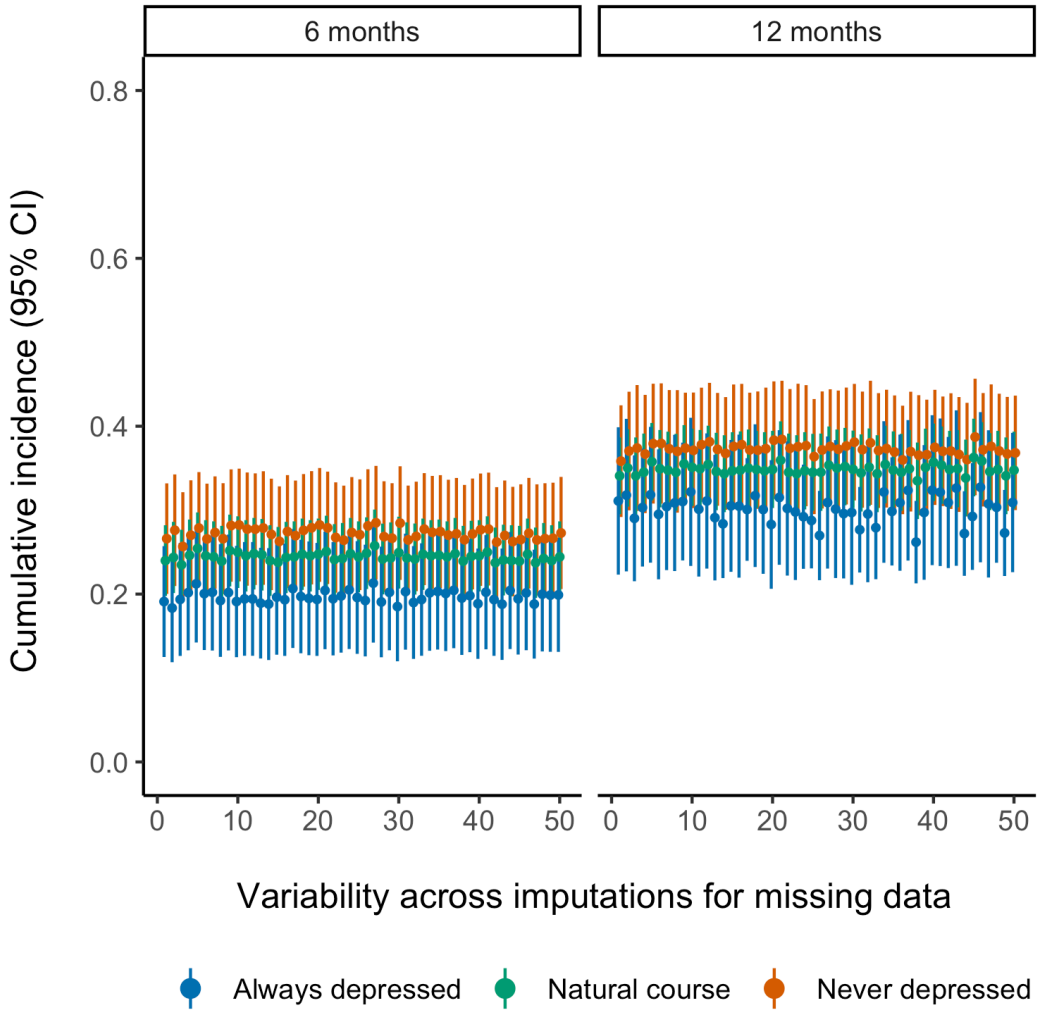


**Figure 5.6. Cumulative incidence of viral suppression, by imputation.**

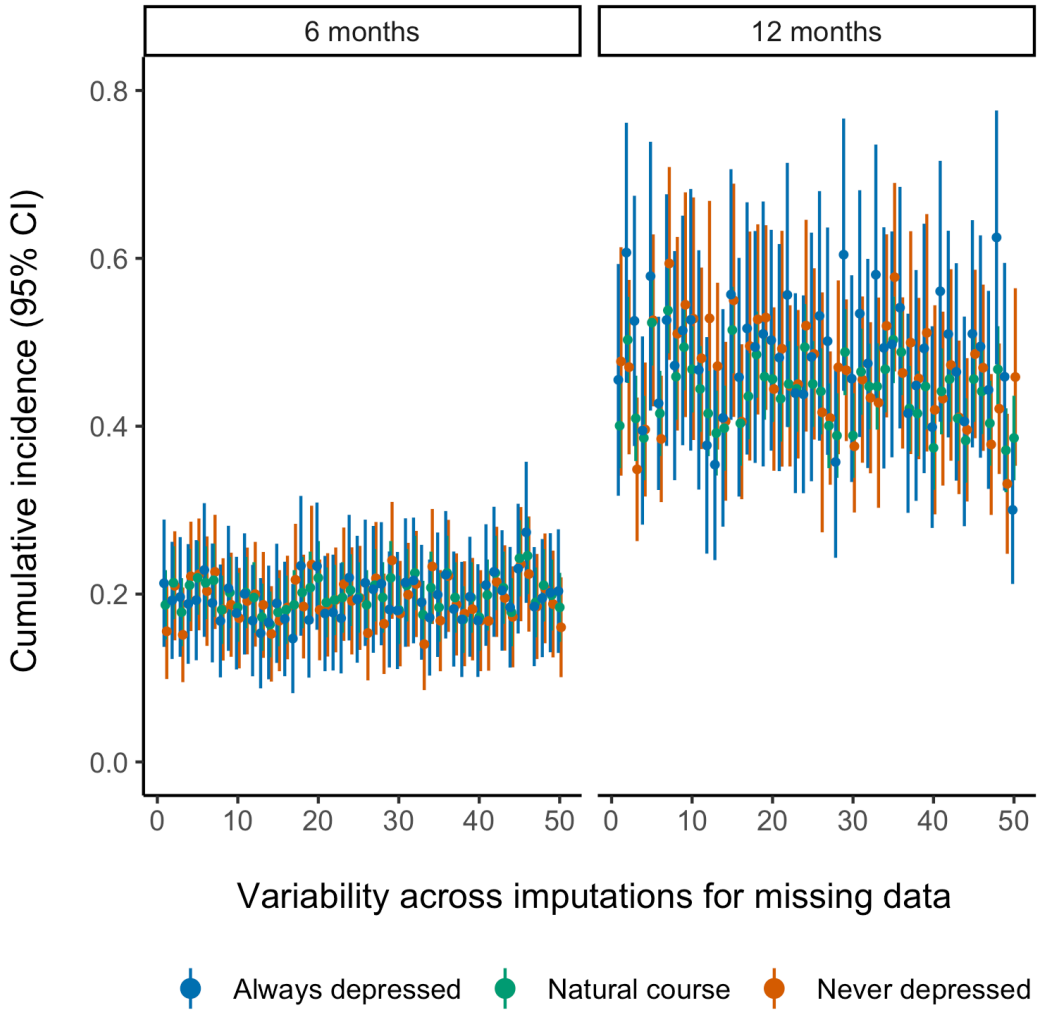


**Figure 5.7. Cumulative incidence differences for ART initiation, by imputation, contrasting always depressed vs. never depressed.**

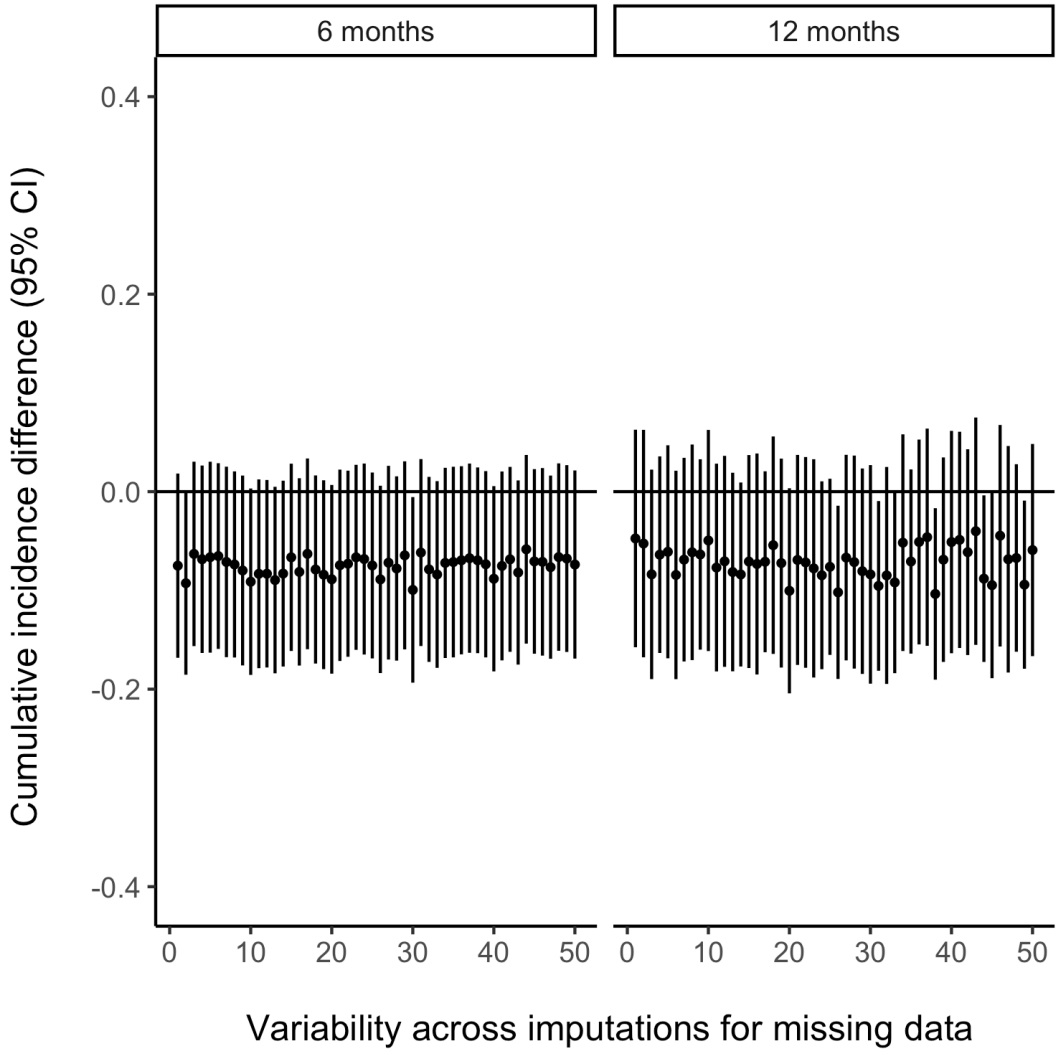
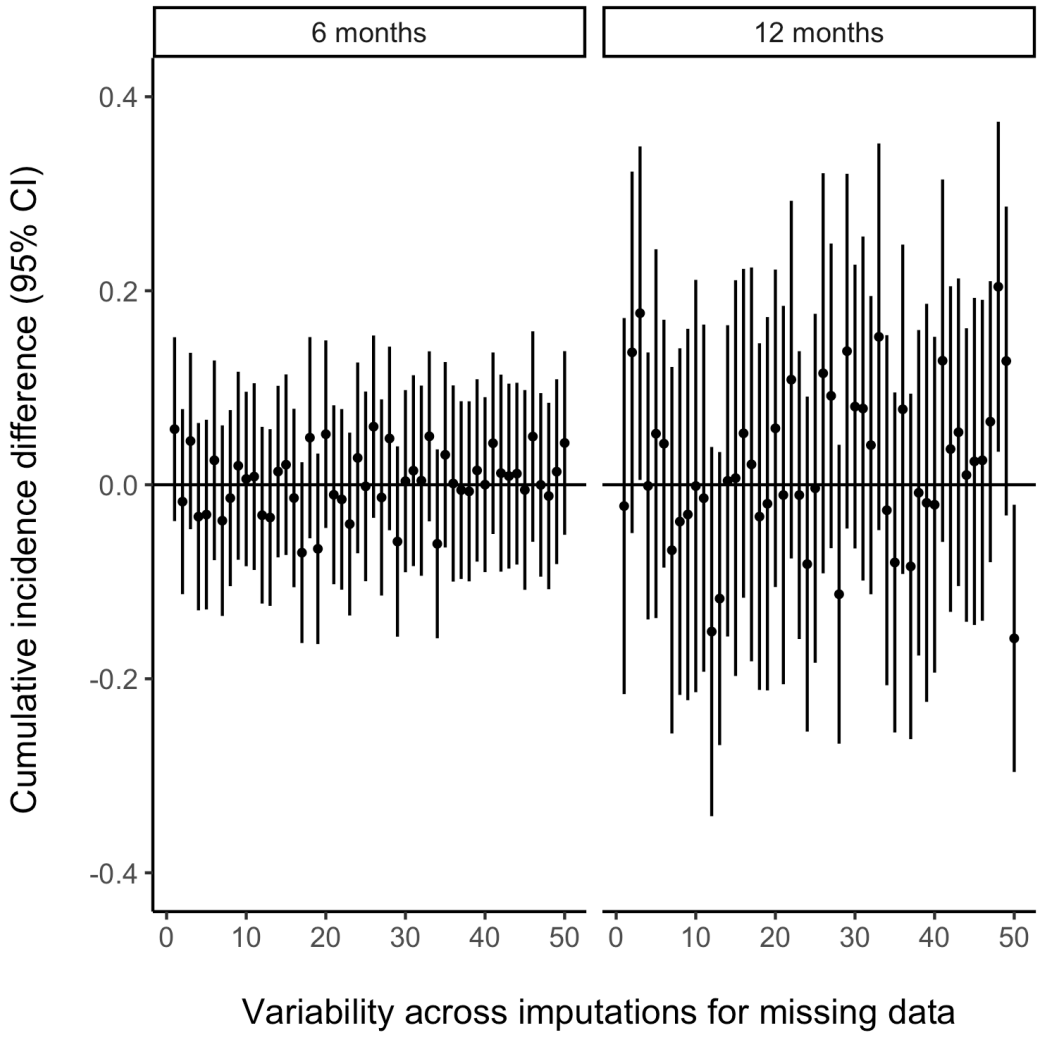


**Figure 5.8. Cumulative incidence differences for viral suppression, by imputation, contrasting always depressed vs. never depressed.**



# CHAPTER VI: THE ROLE OF DEPRESSION IN HIV TRANSMISSION AMONG PEOPLE WHO INJECT DRUGS IN VIETNAM: A MATHEMATICAL MODELING ANALYSIS

## Introduction

Sharing drug preparation and injection equipment is one of the most efficient means of HIV acquisition and transmission (4,5), yet coverage of harm reduction services for most people who inject drugs (PWID) remains inadequate (2,9,10). For PWID living with HIV, barriers to HIV care engagement and antiretroviral therapy (ART) use can inhibit viral suppression, resulting in onward HIV transmission to injecting partners (8–10). Equipment sharing in the absence of viral suppression continues to sustain the HIV epidemic among PWID, particularly in Asia and eastern Europe (11,12).

Depression could be an underlying cause of HIV transmission among PWID. Up to 50% of PWID suffer from severe depressive symptoms (16–20), and depression has been linked to both increases in sharing behaviors (36,38–40) and decreases in ART initiation and viral suppression (26,28–32). Despite evidence supporting these links, the role of depression in HIV transmission among PWID has not been quantified. Prior research has focused on individual components of transmission risk (i.e., sharing behaviors or viral load) but has not investigated the overall contribution of depression to HIV transmission through the combination of these behavioral and biological pathways.

In this study, we use mathematical modeling to estimate secondary HIV transmission events from PWID living with HIV to their potentially susceptible injecting partners. We base input parameter values on behavioral and viral load data from PWID

living with HIV in Vietnam, where injection drug use drives the HIV epidemic (58,59,145). Given continued HIV incidence among PWID (8,11) and the plausible role of depression, it is critical to better understand how depression may drive onward transmission and the extent to which successful depression treatment could avert future infections.

## Methods

### Study Population

We modeled parenteral HIV transmissions arising from 455 adult, male PWID enrolling in a randomized controlled trial of an HIV prevention intervention in Thai Nguyen, Vietnam from 2009 to 2013. Trial details have been published previously (45), but briefly, participants were recruited via snowball sampling from the 32 sub-districts of Thai Nguyen with the most PWID. The intervention included structural and individual components, with randomization occurring at the sub-district level for the former and the individual level for the latter. The structural intervention aimed to reduce community-level HIV and injection drug use stigma, and the individual intervention provided support to participants in coping with HIV and reducing both condomless sex and sharing of injection drug use equipment. The randomization process resulted in four trial arms: individual intervention only, structural intervention only, combined intervention (both individual and structural), and control (standard of care). As previously reported (45), no differences in injecting or sexual behaviors across intervention arms were observed over 24 months in the trial.

**Measures**

Participants enrolled in the trial responded to a questionnaire in face-to-face interviews at baseline and follow-up visits at 6, 12, 18, and 24 months. At each interview, participants were asked to name up to ten partners with whom they had injected drugs in the prior three months, and for each partner, to report the frequency in those three months of: 1) sharing the same needle or syringe, 2) sharing drug solution, and 3) sharing the same ampoule of distilled water or novocaine. Participants were also asked if each partner had HIV, with possible responses being “Yes”, “No”, or “Don’t know”.

In the parent trial, blood specimens were collected to confirm HIV infection at baseline and to measure CD4 cell count at all visits. To obtain viral load data for the current analysis, we performed HIV RNA testing on stored plasma specimens using COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test platform (Roche Diagnostics GmbH) with a lower limit of detection of 20 copies/mL. Due to insufficient volume in >50% of plasma samples from the 12-, 18-, and 24-month visits, we limited the scope of our analysis to data collected at the baseline and six-month follow-up visits.

The trial questionnaire also assessed depressive symptoms in the past week with the Center for Epidemiologic Studies Depression Scale (CES-D), which has been validated in Vietnam (50). Consistent with past work in this population (20,46,50,51), we defined severe depressive symptoms as CES-D scores ≥23, mild depressive symptoms as scores 16-22, and no symptoms as scores <16.

**Model Equations**

We developed a modified Bernoulli process mathematical model (99,115–118) to estimate the expected number of secondary HIV transmission events from each study participant in two periods: the three months before baseline and the three months before the six-month visit. Transmission estimates were based on viral load measurements taken at the end of a given period, reported numbers of injecting partners in the period, sharing acts within those partnerships over the specified period, and reported partner HIV status. With this model (Equation 1), we estimated the probability $P_{ij}$ that study participant $i$ would transmit HIV to named partner $j$ in a specified period, given the probability $\pi_j$ that the partner was already HIV-infected at the start of that period, the probability $\beta_i$ of HIV transmission in one sharing act with a susceptible partner, and the number of acts $n_{ij}$ between participant and partner over the period.

$$P_{ij} = \left(1 - \pi_j\right)[1 - (1 - \beta_i)^{n_{ij}}] \qquad \text{Equation 1}$$

We specified the per-act transmission probability $\beta_i$ as a function of viral load $v_i$ measured at the end of a given period, an average viral load set-point $v_0$ estimated previously (119), and the transmission probability $\beta_0$ corresponding to that set-point (Equation 2). In this expression, $\beta_i$ increases relative to $\beta_0$ at a rate $\alpha$ per $\log_{10}$-unit increase in viral load $v_i$ above $v_0$ (121).

$$\beta_i = \alpha^{log_{10}(\frac{v_i}{v_0})}\beta_0 \qquad \text{Equation 2}$$

We then estimated $\lambda_i$, the total modeled number of secondary transmissions for each participant $i$ across all partners $j$ in a given three-month period (Equation 3).

$$\lambda_i = \sum_j P_{ij} \qquad \text{Equation 3}$$

Finally, we summed the $\lambda_i$ values for each of the two time periods (the three months prior to baseline and the three months prior to the six-month follow-up visit) for a total number of estimated transmissions across participants in those two windows.

**Model Parameters**

The number of sharing acts ($n_{ij}$) and the probability ($\pi_j$) of partner HIV infection at the start of a given period were based on questionnaire reports at baseline and six months, with $\pi_j$ taking a value of 0 if the partner was reportedly HIV-negative and 1 if a partner was reportedly already HIV-positive. For partners whose HIV status was reported as unknown, we specified $\pi_j$ based on the estimated overall HIV prevalence (34%) among PWID in Thai Nguyen during the study period (57–59). Participant viral load ($v_1$) was fully observed at trial baseline, and for missing viral load due to insufficient samples at six months (31% of participants), we used multiple imputation by chained equations (113,114) to impute viral suppression status and assign viral load in 50 imputed datasets. We used published estimates in the scientific literature (119–121) for the average viral load set-point ($v_0$ = $\log_{10}$ 4.5 copies/ml), transmission probability per sharing act at that set-point ($\beta_0$= 0.008), and increases or decreases in infectiousness per $\log_{10}$ change in viral load relative to the set-point value ($\alpha$ = 2.09).

Prior modeling work (93–98) has relied on a single per-act probability value that was estimated without specification of (or differentiation by) type of sharing act (120). Given that this transmission probability may be similar across sharing acts (146), we conducted one set of model analyses in which we included all types of sharing acts (needles or syringes, drug solutions, and ampoules of distilled water or novocaine) as potential transmission events, using the single value of $\beta_0$ for all types. Due to

uncertainty about the extent to which the standard probability estimate reflects all acts vs. needle- or syringe-sharing specifically, we also conducted a set of analyses in which we included only needle- or syringe-sharing acts in the model to estimate a lower bound on modeled transmissions.

**Modeling Analysis**

To incorporate uncertainty around model inputs into our model outputs, we ran the model 50 times for each of 50 imputed datasets (2,500 model runs total). In each model run, we drew values for $\pi_j$ (for partners with unknown HIV status), $\alpha$, and $\beta_0$ from the distributions specified by their published summary estimates and confidence limits. Participants were excluded from the analysis at six months if they experienced a competing event between baseline and six months (12% died or incarcerated) or missed the 6-month visit not due to a competing event (5%).

To evaluate differences in predicted transmission events by depression, we stratified the population according to baseline depressive symptoms (severe, mild, or no symptoms) and compared the total number of estimated transmissions by depressive symptom group, the probability of infection per partner, and the number of estimated transmissions per participant. To account for different sample sizes by depression, we weighted the number of total transmissions such that each group was upweighted to stand in for the full study population (e.g., transmissions for 202 participants with severe symptoms were multiplied by 2.25 [total sample size N=455 divided by depression group n=202]). Since depressive symptoms were assessed at both baseline and six months, we conducted a secondary analysis of 6-month transmission by 6-month depressive symptoms (instead of baseline depressive symptoms).

To account for possible misreporting of partner HIV status, we performed a sensitivity analysis in which a random sample of 25% of partner HIV status reports of "Positive" or "Negative" in each model run were assumed to be inaccurate (i.e., status was reversed for 25% of partners reported to be HIV-positive or HIV-negative). We also performed a sensitivity analysis around the assumed relationship between viral load and the transmission probability, as the current estimate for $\alpha$ is based on sexual transmission and may not strictly hold in the context of injection drug use. For this analysis, we used a constant transmission probability instead of deriving the probability from viral load measurements (120).

In addition to the transmission model, we performed descriptive analyses on viral load and behavioral data for the overall study population and by baseline depressive symptoms. These analyses included a summary of partner HIV susceptibility, in which we defined "susceptible" partners on the basis of participant reports that the partner was: a) HIV-negative or of unknown HIV status, and b) participating in ≥1 sharing act. For "most susceptible" partners, the participant was also observed to have unsuppressed viral load. Analyses were conducted using R Version 3.4.3 (105).

**Ethics**

The parent trial and this study were approved by the ethical review committees at the Thai Nguyen Center for Preventive Medicine, the Johns Hopkins Bloomberg School of Public Health, and the University of North Carolina at Chapel Hill Gillings School of Global Public Health. Written informed consent was obtained from all participants.

## Results

Among the 455 participants at baseline, the median age was 35 years, almost half (47%) were married or cohabitating, and most (69%) were employed full-time. Most participants (73%) reported sharing injection drug use equipment with partners over the prior three months. Three-quarters (74%) of participants reported no HIV diagnosis before HIV testing at enrollment, and 41% had CD4 cell count less than 200 cells/μL.

### Descriptive Analyses

At baseline, participants had a median viral load of 4.3 $\log_{10}$ copies/mL and reported a total of 833 injecting partners (average of 1.8 per participant) in the prior three months; most partners were reported to have unknown HIV status (45%) or to be HIV-negative (30%) (Table 6.1). On average, participants reported 15.5 sharing acts per partner during the prior three months (primarily sharing ampoules or solutions, rather than needles/syringes). At the six-month visit (i.e., after HIV diagnosis and risk reduction counseling), median viral load decreased to 3.6 $\log_{10}$ copies/mL, and the total number of injecting partners over the prior three months dropped an average of 0.7 per participant. Participants reported fewer partners (44%) who were potentially susceptible to HIV (i.e., negative or unknown HIV status) and fewer sharing behaviors (mean 4.3 acts per partner during the prior three months).

At both baseline and six months, there were few clear differences in viral load or sharing behaviors according to baseline depressive symptoms. Participants with severe depressive symptoms had both slightly higher viral load and fewer partners who were potentially susceptible to HIV (compared to mild or no symptoms), whereas participants with mild depressive symptoms reported somewhat higher numbers of sharing acts per

partner (compared to severe or no symptoms). However, estimates were imprecise and confidence intervals overlapped heavily.

At baseline, 333 of 833 partners (40%) were considered to be most susceptible to HIV (Figure 6.1). This portion decreased to only 20 of 251 partners (8%) at six months. When stratified by index participants' baseline depressive symptoms, these most susceptible partners were more likely to be reported by participants with severe symptoms at baseline, but by participants with mild symptoms at six months.

**Modeling Analyses**

Across 2,500 model runs, we estimated a median of 41.2 ($2.5^{th}$, $97.5^{th}$ percentiles: 33.2, 49.2) secondary transmissions from all reported sharing acts with 833 injecting partners in the three months prior to the baseline visit. This estimate fell to 3.0 (2.2, 3.8) transmissions when only needle- or syringe-sharing acts were modeled. For 251 partners reported at six months, we estimated a median of 1.2 (0.8, 1.7) transmissions in the prior three months based on all sharing acts and 0.1 (0.0, 0.2) based only on needle- or syringe-sharing.

The highest numbers of secondary transmissions were predicted for participants with severe depressive symptoms across time periods and types of sharing acts modeled (Figures 6.2, 6.3). In the three months prior to baseline, 45.7 (36.7, 54.7) transmissions from all reported sharing acts were predicted to arise from the study population had all 455 participants experienced severe depressive symptoms; this decreased to 39.6 (31.0, 49.8) transmissions if all participants experienced mild symptoms and 35.9 (28.8, 42.8) transmissions if all participants experienced no symptoms. When modeled transmissions were restricted to needle- or syringe-sharing

acts, these estimates decreased to 4.9 (3.3, 6.7) transmissions for severe symptoms, 2.0 (1.4, 2.9) transmissions for mild symptoms, and 1.0 (0.8, 1.2) transmissions for no symptoms.

In follow-up months 3-6, secondary transmissions modeled for all sharing acts fell to 1.9 (1.1, 2.8) had all participants experienced severe symptoms, 1.3 (0.8, 2.1) for mild symptoms, and 0.2 (0.1, 0.5) for no symptoms. Estimates further decreased when only needle- or syringe-sharing acts were modeled; non-zero transmissions were predicted only for participants with severe symptoms. These results were consistent regardless of whether the baseline or 6-month depressive symptom measure was used (Figure 6.4).

When we accounted for possible misreporting of partner HIV status, there was greater uncertainty in transmission estimates but differences by depression were similar (Figures 6.5, 6.6, 6.7). When we assumed a constant transmission probability regardless of viral load, greater transmissions at baseline were predicted for participants with mild symptoms vs. those with severe symptoms, possibly reflecting participants with mild symptoms who reported sharing behaviors with susceptible partners but had low or suppressed viremia at that time (Figures 6.8, 6.9, 6.10).

The majority of modeled transmissions arose from a small number of participants. Given that most participants had zero predicted transmissions, the mean probability of infection per partner and the mean transmission events per participant were heavily weighted towards zero regardless of depressive symptoms. When modeling transmission using all sharing acts reported at baseline, the mean probability of infection per partner was 0.05 for each depressive symptom group. This mean

probability fell to near-zero when only needle- or syringe-sharing acts were modeled at baseline and regardless of type of sharing act at six months. However, there were notable outliers with higher mean probability values per partner, particularly for partners of participants with severe depressive symptoms (Figure 6.11). The mean transmissions per participant ranged from 0 to 3 across time points, types of sharing acts, and depressive symptoms. The small number of participants with non-zero predicted transmission events disproportionately had severe depressive symptoms (Figure 6.12).

**Discussion**

In this study of PWID living with HIV in Vietnam, we used mathematical modeling to estimate secondary HIV transmission events from PWID to their potentially susceptible injecting partners. A high number of secondary transmissions was predicted for the three months prior to study baseline when transmission was modeled for all reported sharing behaviors (sharing ampoules, solutions, and needles/syringes); this estimate dramatically decreased when only needle- or syringe-sharing behaviors were modeled. These disparate findings demonstrate the sensitivity of model estimates to the assumed infectivity of different sharing behaviors, a phenomenon that has not been routinely considered in prior modeling studies of injection-related HIV transmission. Due to substantial declines across all reported sharing behaviors after baseline, we estimated that very little secondary transmission occurred during follow-up months 3-6.

Prior research has linked depression to increased sharing behaviors (36,38–40) and decreased ART initiation and viral suppression (26,28–32), and in the current analysis, we found some evidence of greater secondary transmissions for PWID with depression. Across analyses, the highest numbers of total secondary transmissions

were predicted for participants with severe depressive symptoms. However, there was substantial variability in the magnitude of differences across model simulations, time points assessed, and specific risk behaviors modeled. The majority of modeled transmissions arose from only a small number of participants, resulting in group averages of the probability of infection per partner and transmission events per participant being heavily weighted towards zero regardless of depressive symptoms. Given the multi-faceted nature of transmission, it is plausible that depression has a combination of synergistic and antagonistic effects, the net sum of which are the small increases in projected transmission observed in this modeling analysis.

We expect that our model predictions underestimate all true transmissions arising from this population during the study period. Our model relied on self-reported sharing behaviors, and social desirability bias may have led to underestimates of these sensitive behaviors. Due to the time horizon specified in the questionnaire, our model predictions do not capture the first three months following baseline. In addition, missing data precluded transmission estimates for participants who experienced a competing event between baseline and six months or who missed the 6-month visit for other reasons. Further, we focused on transmission to injecting partners, excluding sexual transmission. However, condomless sex was reported infrequently among participants, so the exclusion of sexual transmission is not expected to have had a substantial impact on transmission estimates. We additionally note that our model assumes that viral load measures taken at baseline and six months applied to the prior three months, which might have been especially likely to underestimate transmission in the second interval, when viral loads were more likely to have been decreasing over time due to diagnosis

and treatment. Finally, we note that our model only predicts secondary transmissions over a very limited period of time, and does not estimate transmission events arising from partners of participants.

Despite underestimating transmission, our modeling projections suggest a disproportionate burden of severe depressive symptoms among those few participants from whom transmissions were predicted to arise. To investigate the extent to which successful depression treatment could avert future infections, future modeling work could simulate potential intervention scenarios to decrease depressive symptoms and subsequently lower sharing behaviors and viral load (as informed by this study). Models could vary the coverage and efficacy of interventions to more realistically reflect depression screening and treatment approaches that could be implemented among PWID. Depression treatment could be modeled alongside other current prevention interventions (ART, needle exchanges, methadone maintenance) to understand the optimal combination of these approaches in decreasing HIV incidence among PWID. More generally, future models of injection-related HIV transmission should examine uncertainties in the infectivity of different sharing behaviors and the relationship between viral load and transmission probability in the context of injection drug use. These assumptions substantially influenced this study's transmission estimates and are understudied phenomena with important implications for our understanding of HIV transmission among PWID.

While the net contribution of depression to onward transmission did not appear substantial, there was a skewed distribution of transmissions by depression status, with greater secondary transmissions predicted for participants with severe depressive

symptoms. Our findings reflect a complex relationship of depression with HIV transmission, and further modeling analyses could investigate the potential impact of depression interventions on continued HIV incidence among PWID. Depression interventions may further decrease the small number of participants with estimated secondary transmissions, in addition to providing widespread mental health benefits for this PWID population.

**Table 6.1. Characteristics of study population associated with HIV transmission risk.**

| | Overall N = 455 | Baseline depressive symptoms: Severe n = 202 | Mild n = 115 | None n = 138 |
|---|---|---|---|---|
| **Baseline characteristics** | | | | |
| Median (IQR) participant viral load | 4.3 (2.6, 4.9) | 4.5 (3.1, 5.0) | 4.1 (1.9, 4.7) | 4.4 (2.2, 4.9) |
| Number of injecting partners (last 3 months) | 833 | 400 | 211 | 222 |
| Partner HIV status (% of partners) | | | | |
| Reported to be HIV-negative | 30% | 29% | 26% | 36% |
| Reported to be unknown | 45% | 43% | 49% | 47% |
| Mean (range) acts per partner (last 3 months) | | | | |
| Sharing ampoules | 5.5 (0, 90) | 5.4 (0, 90) | 5.8 (0, 90) | 5.6 (0, 90) |
| Sharing solutions | 9.1 (0, 90) | 9.1 (0, 90) | 9.3 (0, 90) | 8.9 (0, 90) |
| Sharing needles or syringes | 0.9 (0, 30) | 1.1(0, 30) | 1.2 (0, 30) | 0.4 (0, 30) |
| **6-month characteristics** | | | | |
| Number (%) for follow-up | | | | |
| Attended visit | 377 (83%) | 158 (78%) | 97 (84%) | 122 (88%) |
| Missed visit: competing event | 55 (12%) | 39 (19%) | 8 (7%) | 8 (6%) |
| Missed visit: no competing event | 23 (5%) | 5 (2%) | 10 (9%) | 8 (6%) |
| Median (IQR) participant viral load* | 3.6 (1.8, 4.5) | 3.8 (2.0, 4.6) | 3.4 (1.8, 4.3) | 3.7 (1.6, 4.5) |
| Number of injecting partners (last 3 months) | 251 | 117 | 69 | 65 |
| Partner HIV status (% of partners) | | | | |
| Reported to be HIV-negative | 24% | 31% | 17% | 17% |
| Reported to be unknown | 20% | 15% | 20% | 31% |
| Mean (range) acts per partner (last 3 months) | | | | |
| Sharing ampoules | 1.4 (0, 30) | 1.3 (0, 30) | 1.5 (0, 30) | 1.5 (0, 30) |
| Sharing solutions | 2.5 (0, 30) | 2.1 (0, 30) | 4.8 (0, 30) | 0.7 (0, 30) |
| Sharing needles or syringes | 0.4 (0, 12) | 0.6 (0, 7.5) | 0.2 (0, 7.5) | 0.3 (0, 12) |

* Among 377 participants who attended the 6-month visit, 139 had missing data on viral load due to insufficient sample volume.

**Figure 6.1. Distribution of potentially susceptible partners overall and by baseline depressive symptoms.** Percentages are based on the 833 partners reported by 455 participants at the baseline visit and the 251 partners reported by 377 participants at the 6-month visit.

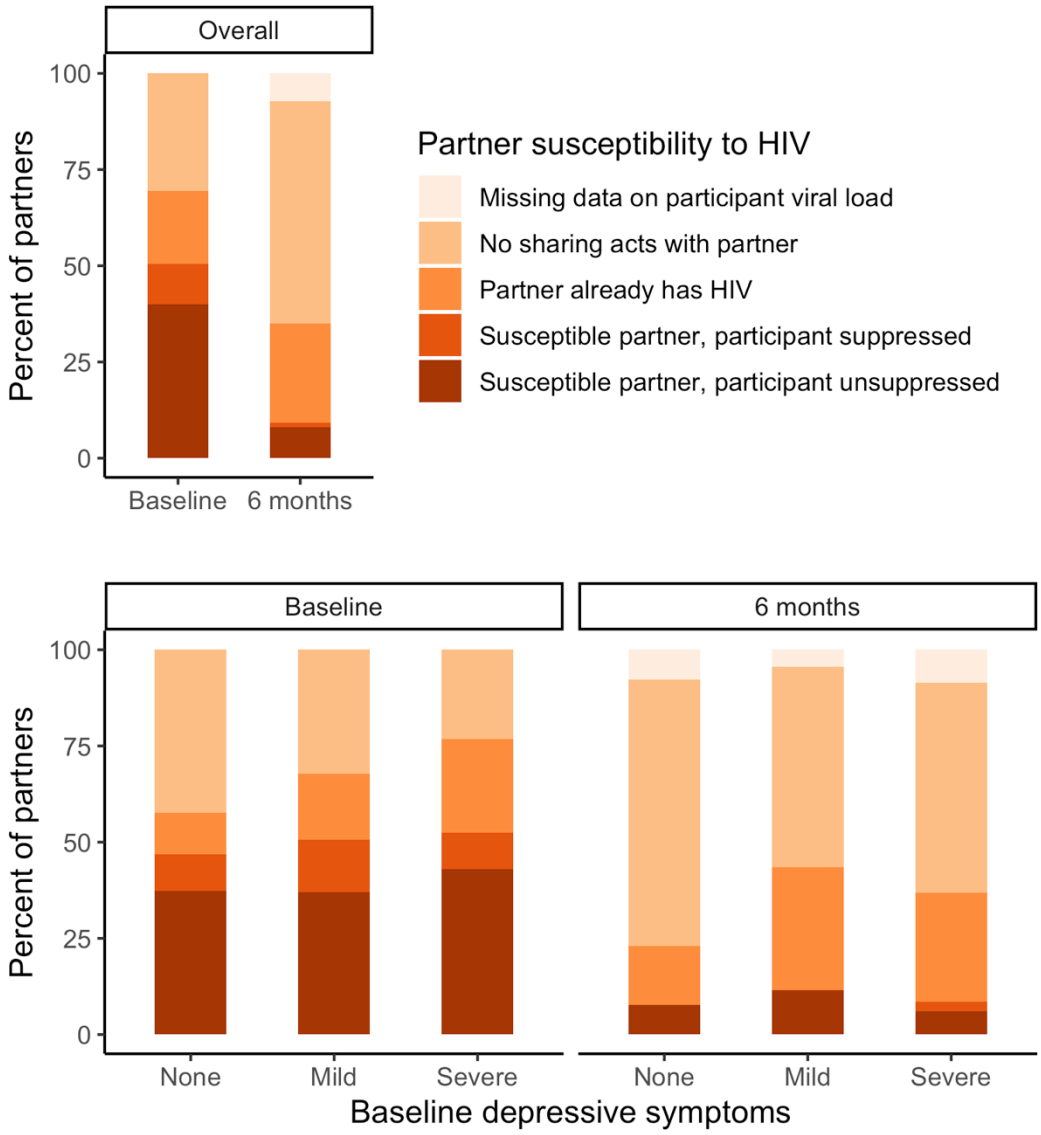


**Figure 6.2. Modeled secondary transmission events in the three months prior to baseline by depressive symptom group.** Each group is upweighted to represent the full study population at baseline (n = 455). Estimates from 2,500 model runs are plotted by type of sharing act (all sharing acts vs. only needle- or syringe-sharing).

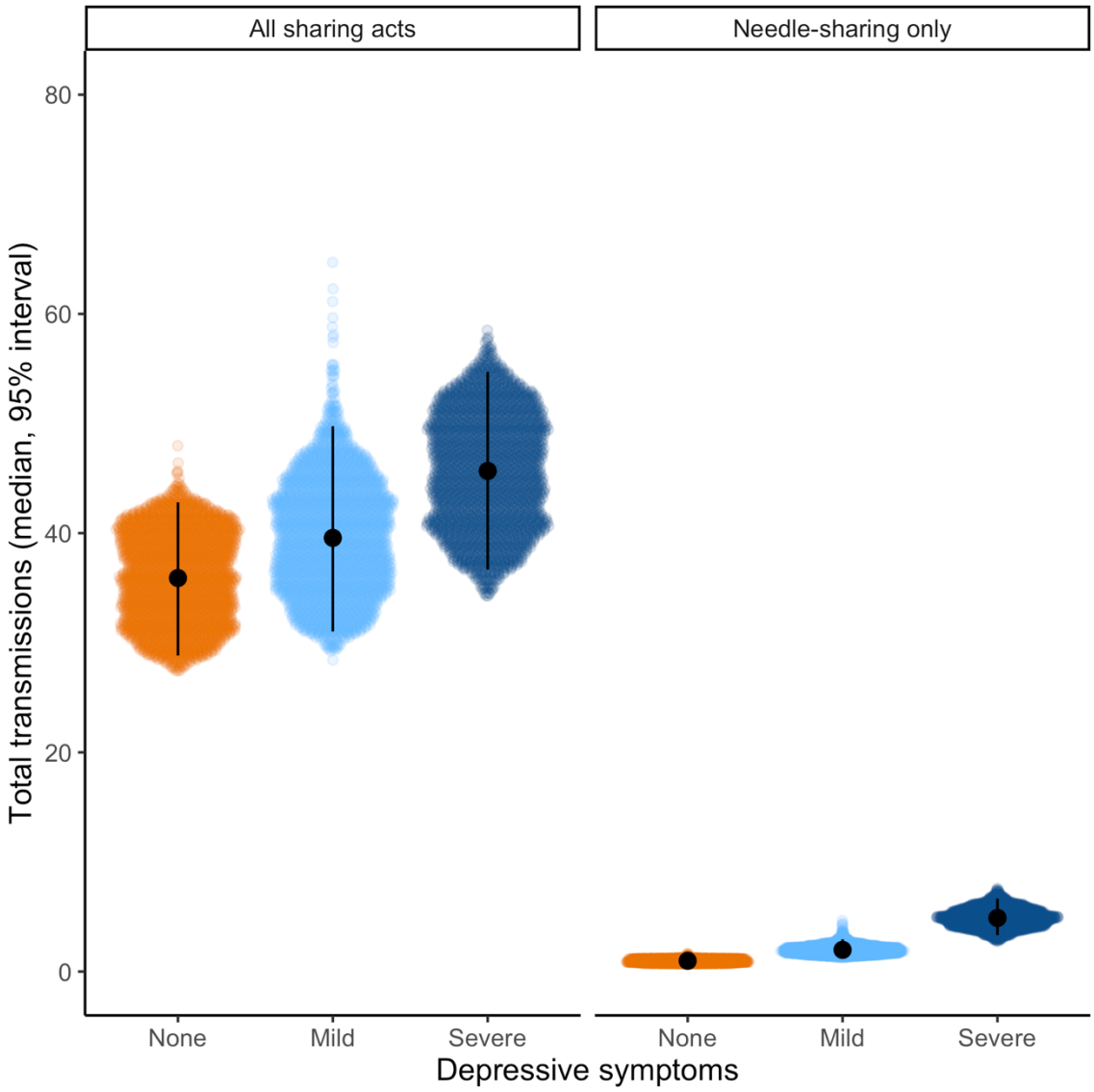


**Figure 6.3. Modeled secondary transmission events in follow-up months 3-6 by depressive symptom group.** Each group is upweighted to represent the full study population at the six-month follow-up visit (n = 377). Estimates from 2,500 model runs are plotted by type of sharing act (all sharing acts vs. only needle- or syringe-sharing).

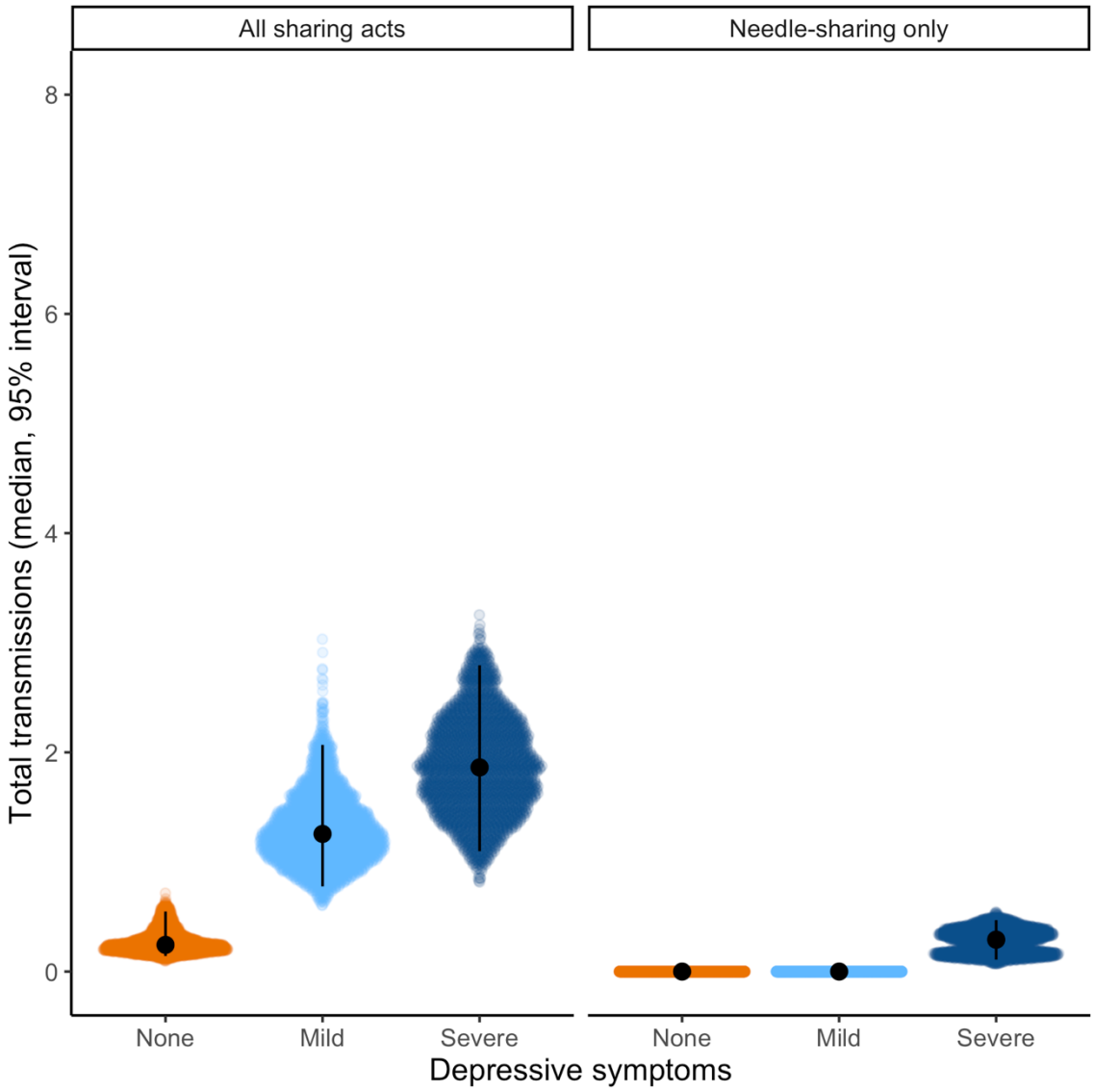


**Figure 6.4. Modeled secondary transmission events in follow-up months 3-6 by depressive symptoms assessed at 6 months (instead of baseline).** Each group is upweighted to represent the full study population at the six-month follow-up visit (n = 377). Estimates from 2,500 model runs are plotted by type of sharing act (all sharing acts vs. only needle- or syringe-sharing).

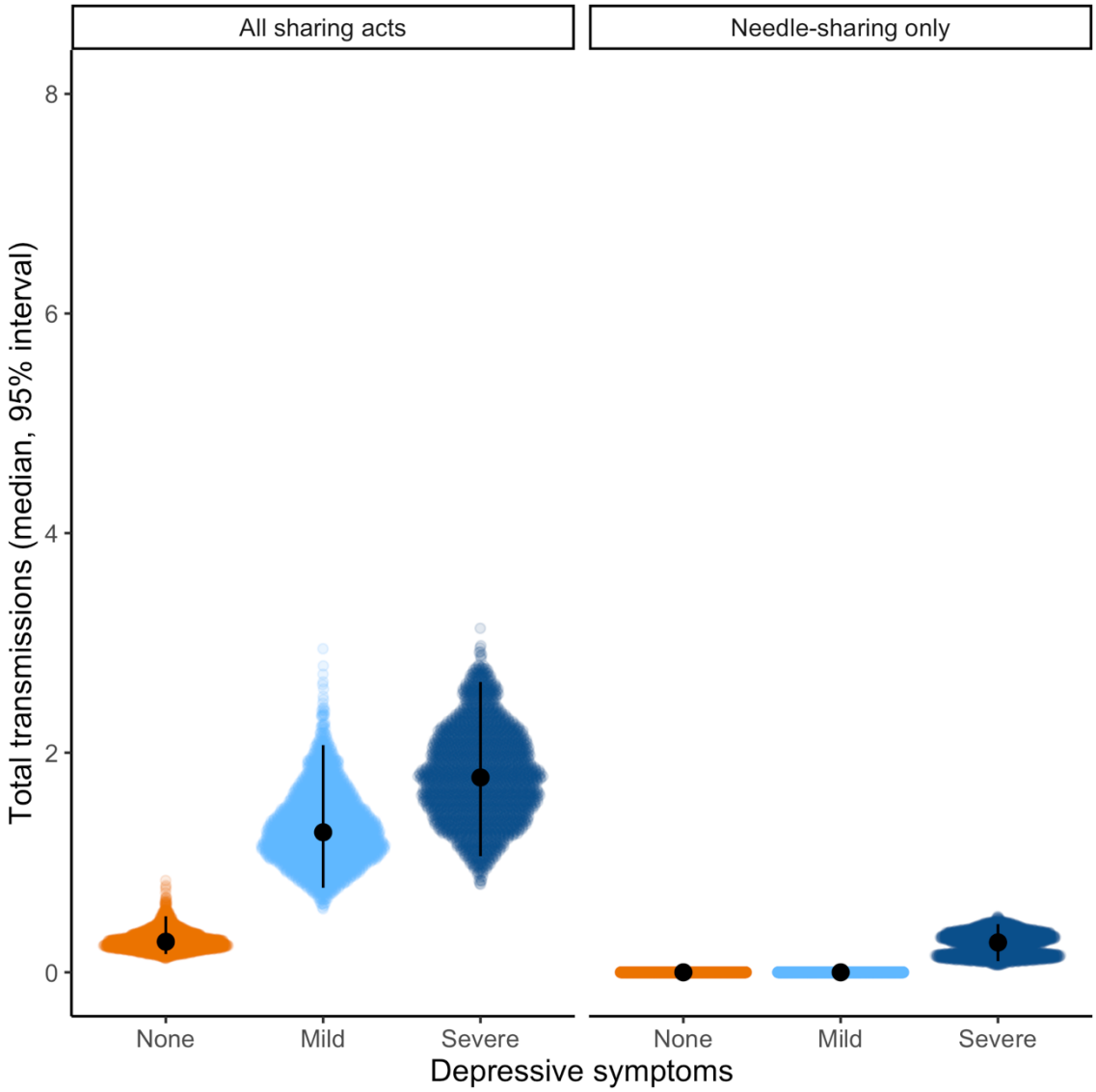


**Figure 6.5. Sensitivity analysis accounting for possible misreporting of partner HIV status (baseline transmission by baseline depression).**

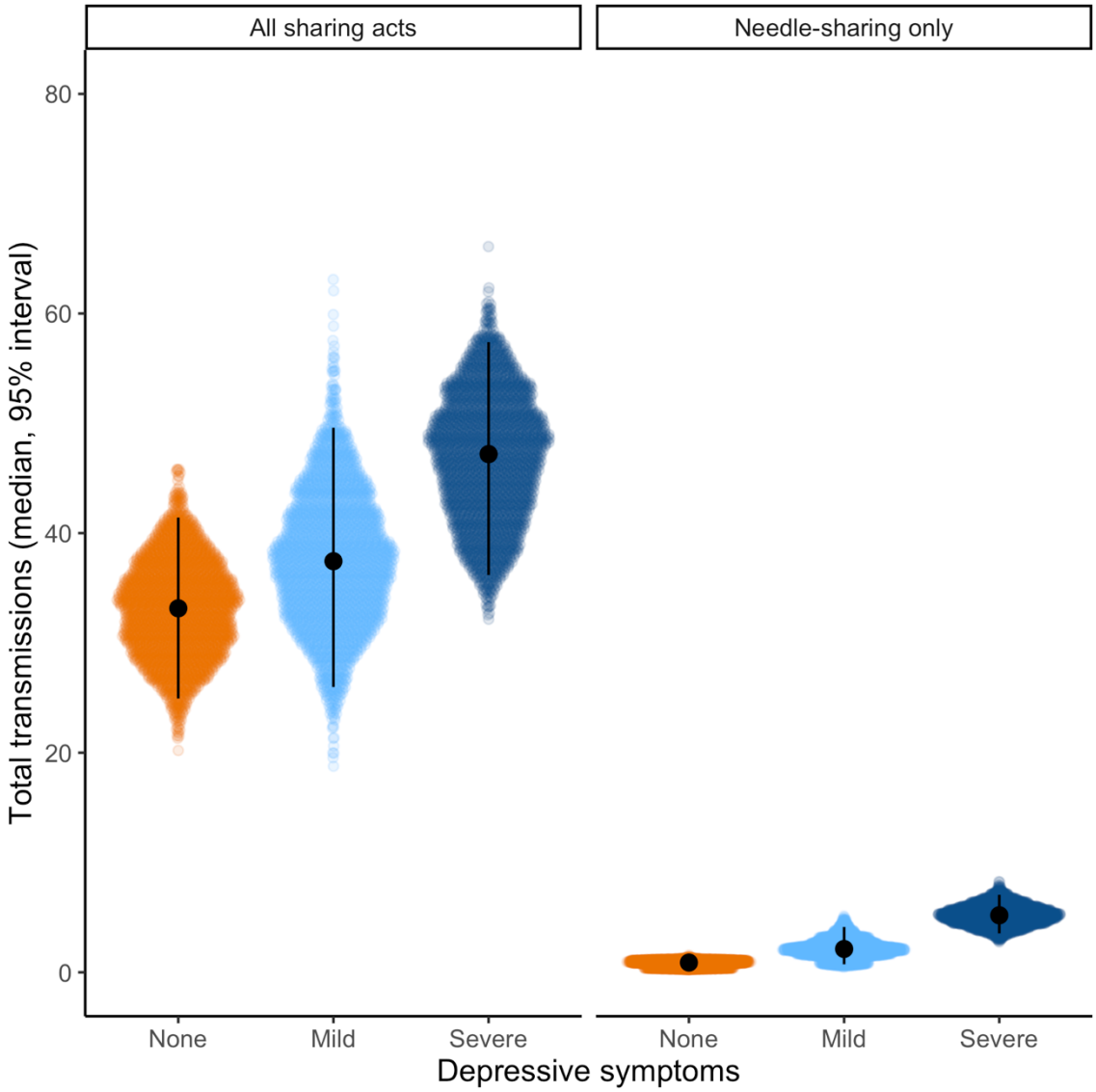


**Figure 6.6. Sensitivity analysis accounting for possible misreporting of partner HIV status (6-month transmission by baseline depression).**

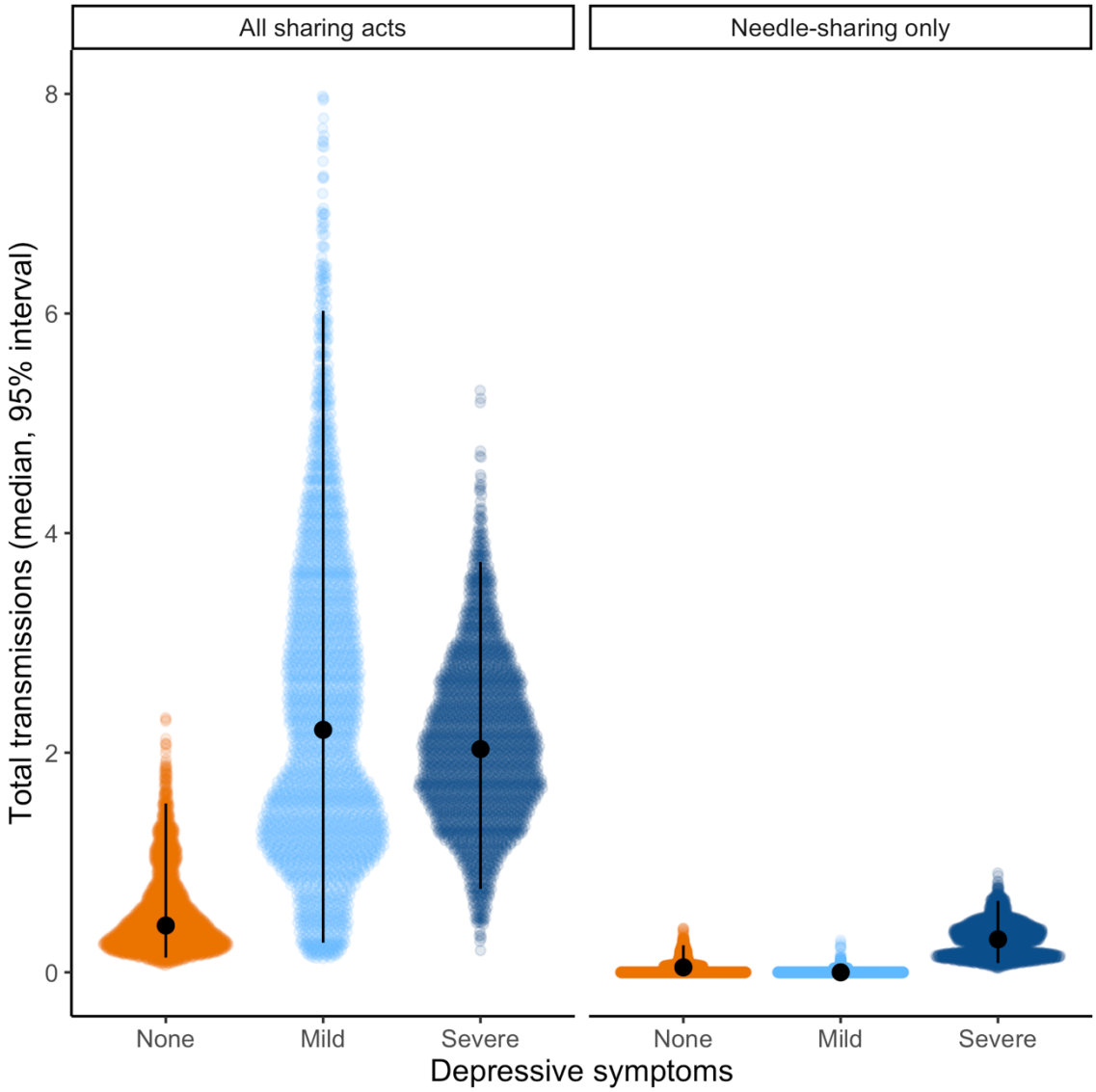


**Figure 6.7. Sensitivity analysis accounting for possible misreporting of partner HIV status (6-month transmission by 6-month depression).**

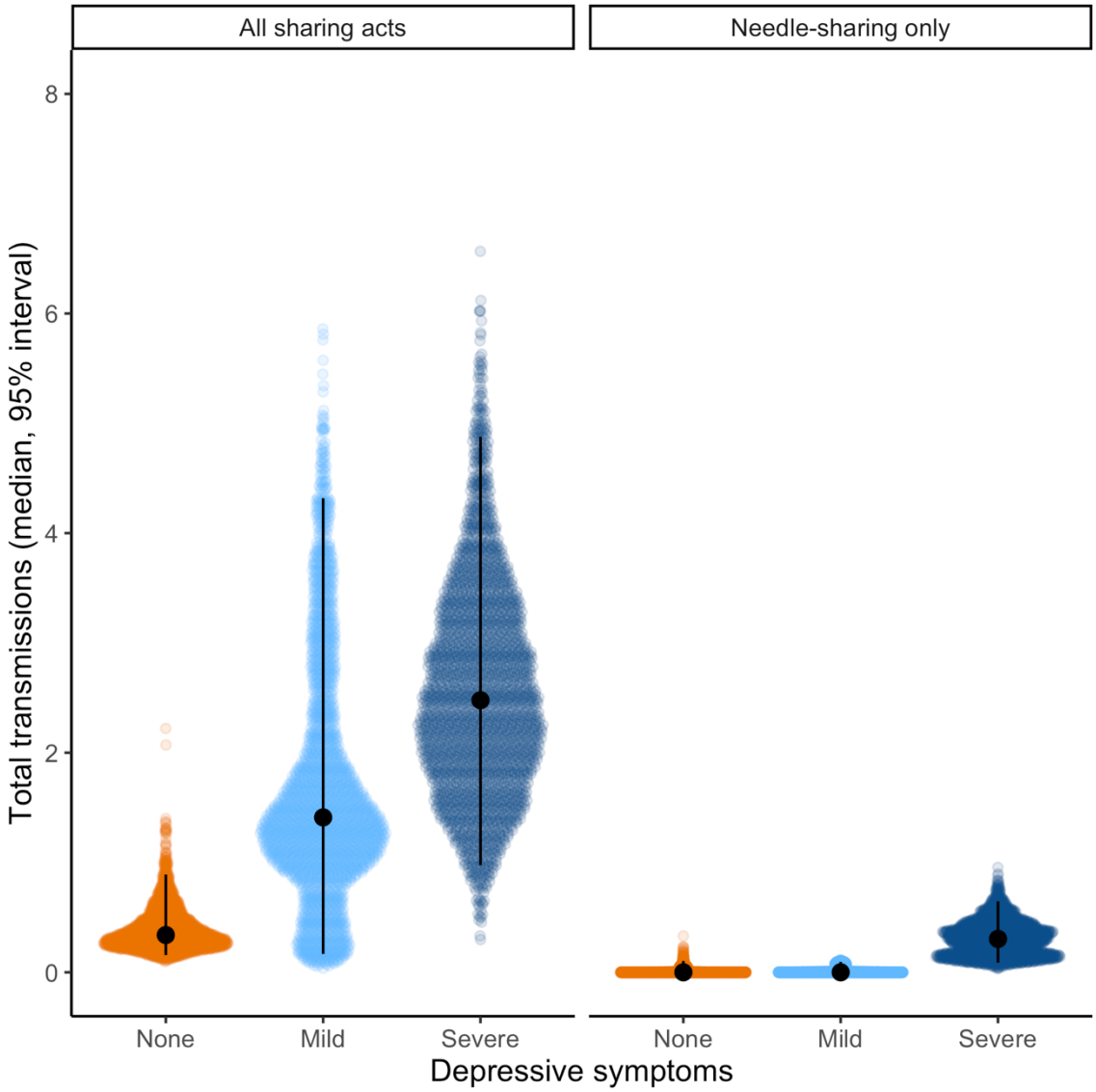


**Figure 6.8. Sensitivity analysis allowing for constant transmission probability (baseline transmission by baseline depression).**

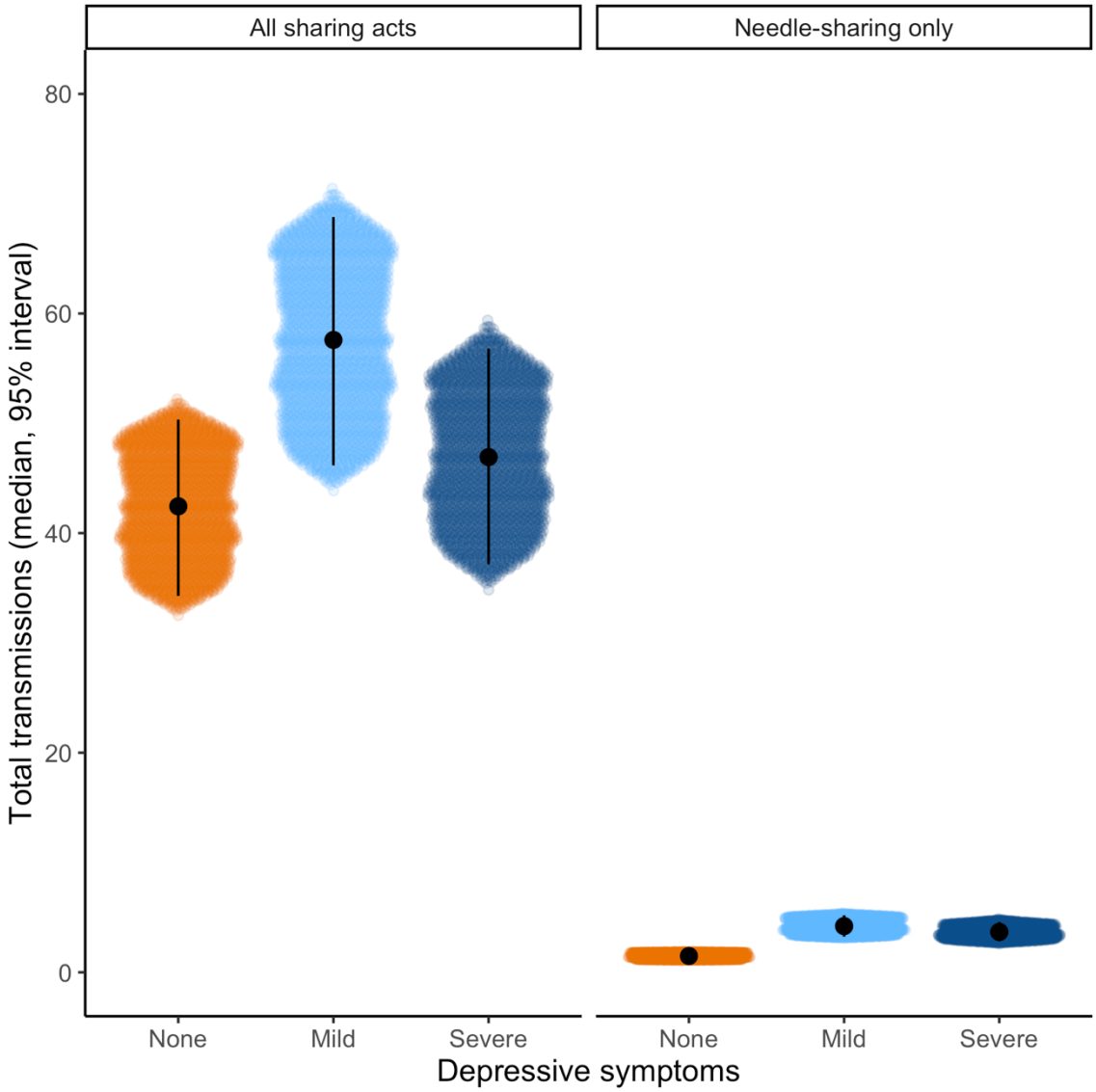


**Figure 6.9. Sensitivity analysis allowing for constant transmission probability (6-month transmission by baseline depression).**

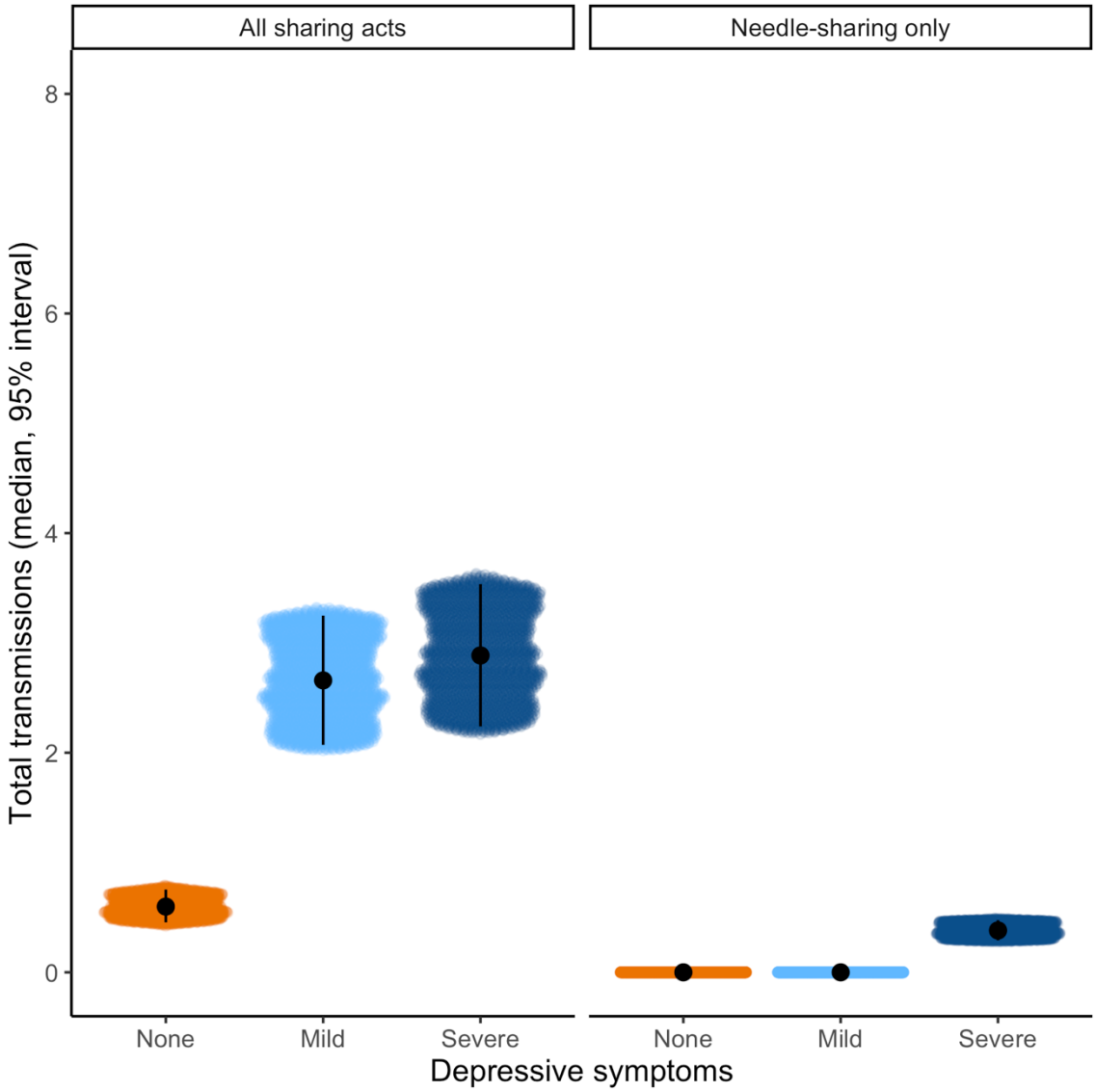


**Figure 6.10. Sensitivity analysis allowing for constant transmission probability (6-month transmission by 6-month depression).**

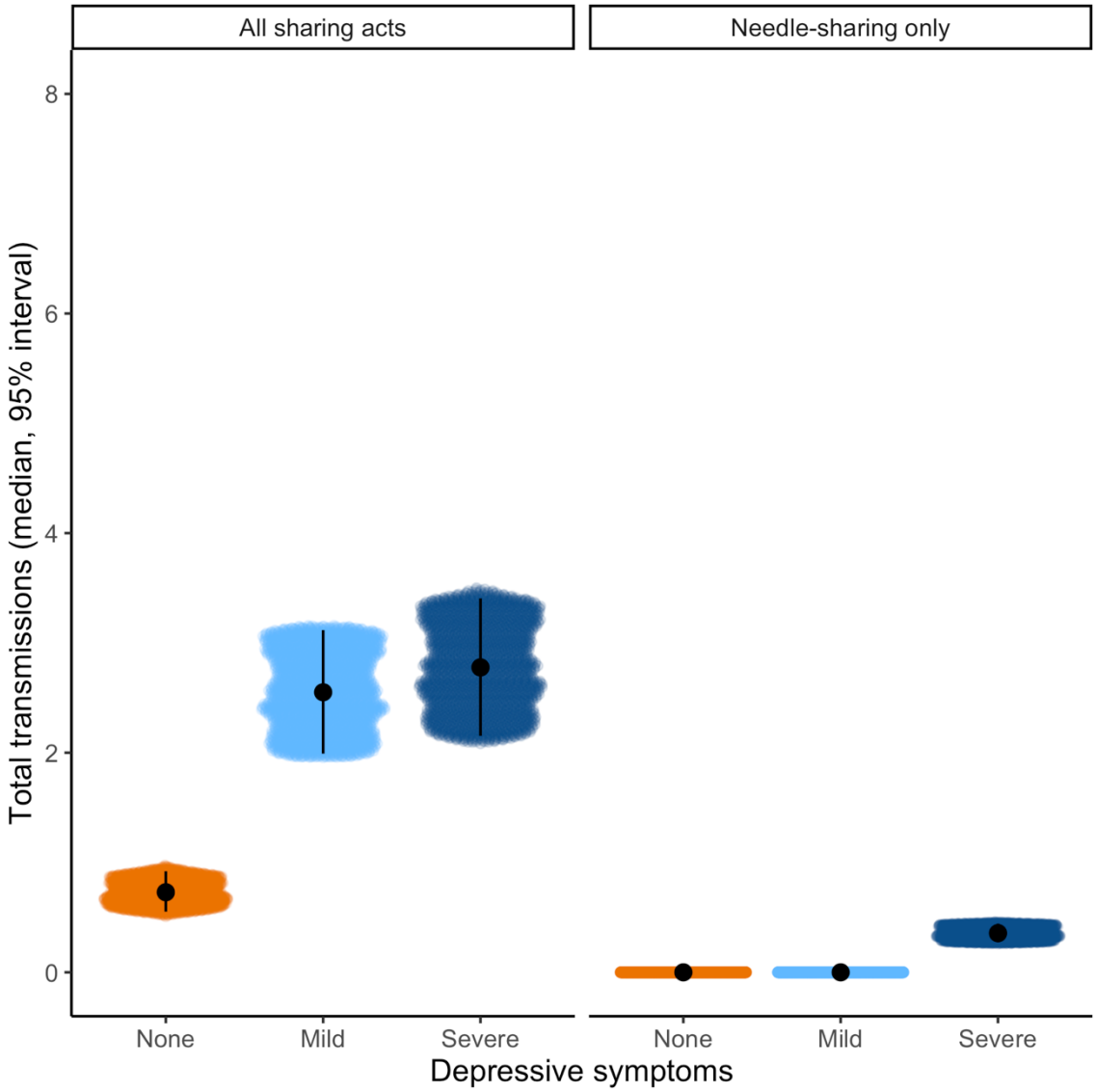


**Figure 6.11. Mean probability of infection (with ranges) for injecting partners reported at baseline and 6 months by depressive symptoms.** Means and ranges are based on 2,500 model runs and are reported separately by the types of sharing acts included in the model (all sharing acts vs. only needle- or syringe-sharing).

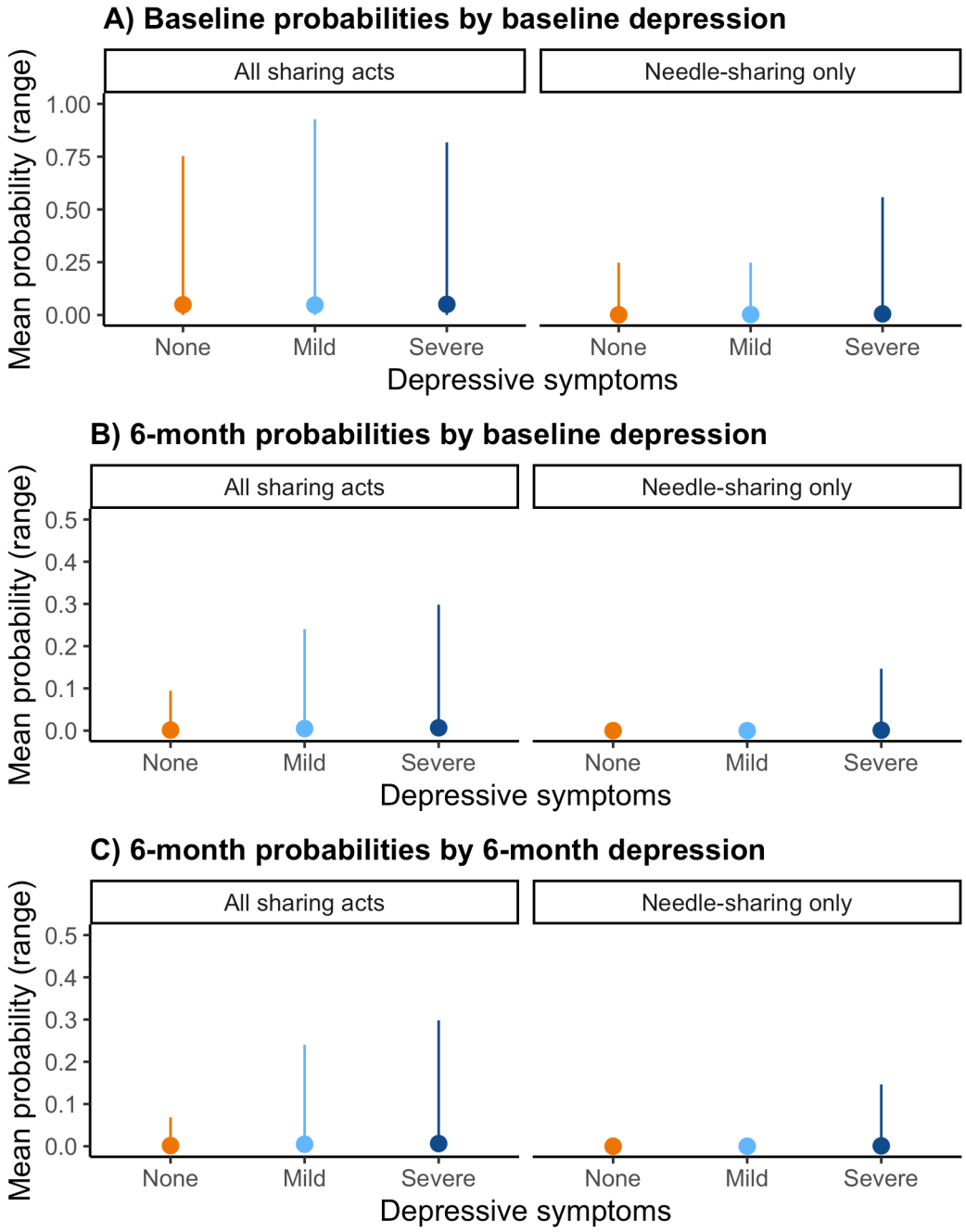
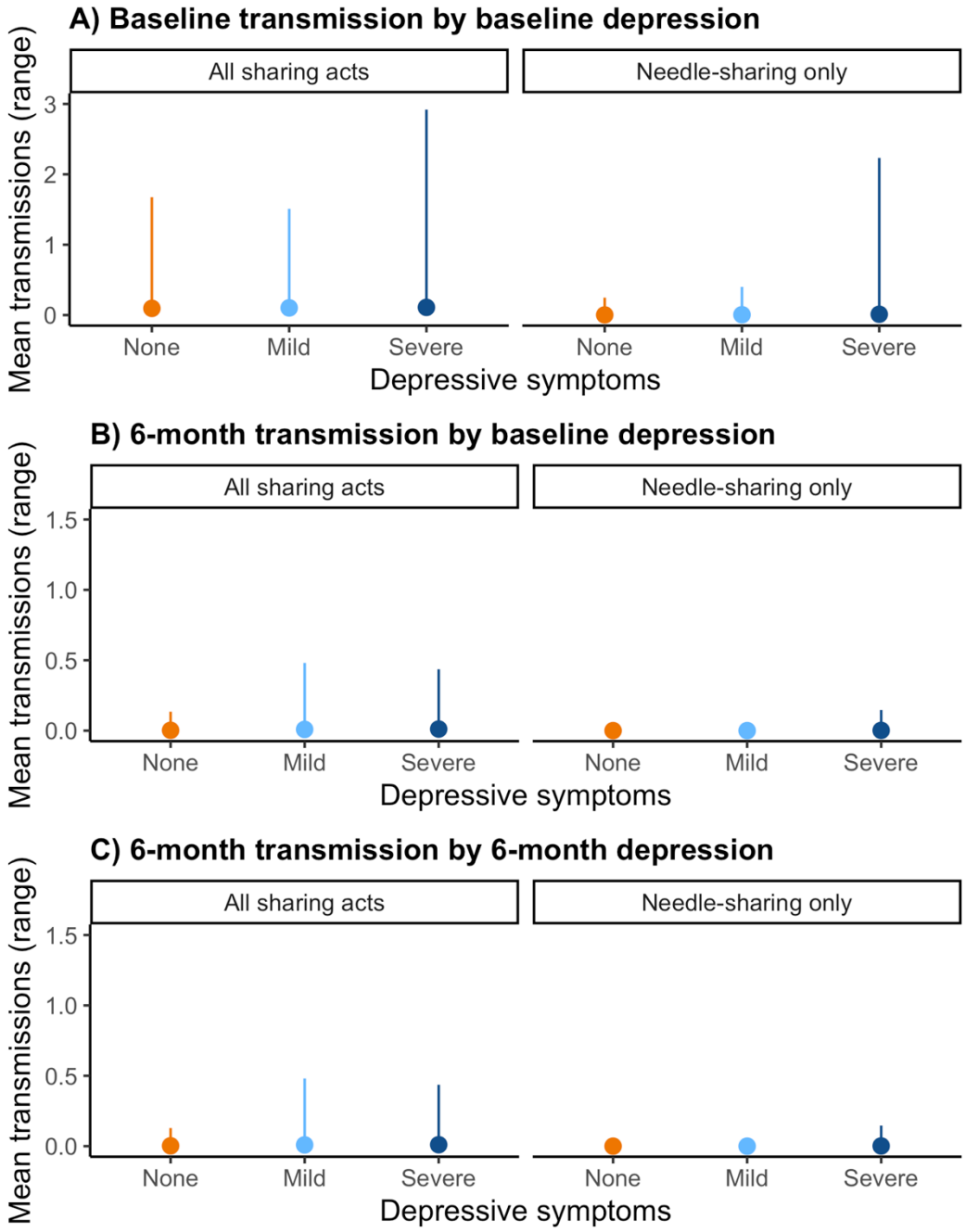


**Figure 6.12. Mean numbers of secondary transmission events (with ranges) per participant at baseline and 6 months by depressive symptoms.** Means and ranges are based on 2,500 model runs and are reported separately by the types of sharing acts included in the model (all sharing acts vs. only needle- or syringe-sharing).



# CHAPTER VII: CONCLUSIONS

## Summary of Findings

This dissertation study was motivated by the disproportionately high burden of HIV and depression among PWID. We sought to better understand the role of depression in perpetuating HIV transmission, hypothesizing that depression increases risk behaviors and uncontrolled viremia, ultimately leading to a higher likelihood of transmission to injecting and sexual partners of PWID. These possible effects of depression were investigated among PWID in Vietnam, a key population in the country's HIV epidemic. Given persistently high HIV incidence among PWID, it is critical to better understand how depression may drive onward transmission and the extent to which successful depression treatment could avert future infections.

This study used longitudinal data collected from 455 PWID living with HIV who enrolled in a randomized controlled trial of a prevention intervention in Thai Nguyen, Vietnam from 2009 to 2013. We combined causal inference methods with mathematical modeling to investigate the individual components of transmission risk (i.e., risk behaviors and viral load) as well as to estimate the overall contribution of depression to HIV transmission through the combination of these behavioral and biological pathways.

In the study population, the prevalence of severe depressive symptoms was 44% at baseline and 33% on average over follow-up visits at 6, 12, 18, and 24 months. In our Aim 1 analysis of depression and transmission risk behaviors, we found that severe depressive symptoms increased the risk of sharing injection equipment but not the risk

of condomless sex over 24 months of follow-up. We also found mixed results in the Aim 2 analysis, in which severe depressive symptoms decreased the cumulative incidence of ART initiation, but not viral suppression, at 6 and 12 months. Combining behavioral and viral load data in the Aim 3 transmission model, we found some evidence of greater secondary transmissions for PWID with depression, albeit with substantial variability across model simulations. A small number of participants were estimated to drive the majority of projected transmission events, but of note, these few participants disproportionately had severe depressive symptoms.

Taken together, our findings suggest that intervening on depression in this PWID population could reduce sharing injection equipment and improve ART uptake, but that other drivers of condomless sex and low viral suppression should be investigated for future intervention. These disparate findings reflect a complex relationship of depression with onward HIV transmission. Given the multi-faceted nature of transmission, it is plausible that depression has a combination of synergistic and antagonistic effects. We found evidence that depression is associated with a higher frequency of injecting partners (Aim 3) and sharing acts within those partnerships (Aims 1 and 3), but that those partners may be more likely to already have HIV (Aim 3). Similarly, while depression leads to lower initiation of ART (Aim 2) and slightly higher viral load (Aim 3), overall incidence of viral suppression did not vary by depression (Aim 2), and small differences in viral load are unlikely to disproportionately drive transmission. While the net contribution of depression to onward transmission did not appear substantial, there was a skewed distribution of transmissions by depression status. Depression interventions may further decrease the small number of participants with estimated

secondary transmissions, in addition to providing widespread mental health benefits for this PWID population.

### Strengths and Limitations

The strengths and limitations of this dissertation are summarized with respect to key threats to the internal and external validity of epidemiological analyses.

### Confounding

The assumption of no unmeasured confounding (i.e., that participants with and without depression are exchangeable) is critical to using observational studies for causal inference. Depression was prevalent among participants at the study start, and there were likely important differences (e.g., HIV disease progression, injection drug use and other substance use, other psychiatric comorbidities) between participants with and without depression that also affected the outcomes of interest. To reduce bias from these preexisting differences, we used a rigorous methodological approach in Aims 1 and 2 to control for a variety of time-fixed and time-varying confounders. However, we did not have measures of all possible confounders and cannot rule out the possibility that unmeasured confounding biased estimates of the effects of depression on transmission risk behaviors, ART initiation, or viral suppression.

### Measurement

Key study variables relied on self-reported data which may be inaccurate due to social desirability bias (e.g., under-reporting of sharing behaviors, over-reporting of ART use or HIV-positive status for susceptible partners) and recall bias (e.g., incomplete reporting of numbers of partners and sharing acts). However, participants reported high levels of (illegal and stigmatizing) drug use; they had also been recruited into the study

by current and former PWID (already aware of the participant's injection drug use), suggesting limited potential for social desirability bias. To aid recall, participants were asked about injecting and sexual behaviors from only the past three months, rather than the full 6-month interval between study visits.

Another possible source of measurement error is this study's use of the CES-D, which indicates probable depression but is not a clinical diagnosis. However, the CES-D has high reliability and validity when compared with psychiatric assessment, including validation among people living with HIV in Vietnam (50). Measurement of depression among PWID is challenging, given that depression may be an antecedent or consequence of injection drug use (74,76), and the short-term effects of drug use reduce negative emotions, such as depressed mood (75). However, the CES-D has been used widely in PWID populations, with strong evidence of its ability to detect high levels of depressive symptoms despite co-occurring drug use (47–49).

**Missingness**

There was substantial missing data on viral load that resulted from insufficient sample volume (<1mL) for stored specimens at follow-up visits: 31% of specimens at 6 months, 59% at 12 months, 48% at 18 months, and 55% at 24 months. Because missingness was thought to occur at random, we used MICE to impute viral suppression (Aim 2) and subsequently assign viral load (Aim 3). However, there was considerable variability across imputations, resulting in imprecise estimates of viral suppression incidence and the potential for bias due to differential missingness by unknown factors. To limit the influence of missing data in this study, we evaluated the viral suppression outcome in Aim 2 at the two earliest follow-up visits (6 and 12

months), and we restricted our focus of the transmission model to only baseline and 6 months. Outside of viral load data, there was very limited missing data on other key study variables.

**Selection**

Our findings are specific to this study sample, which may not be representative of all PWID living with HIV in Vietnam. Although snowball sampling enabled the study team to access a hard-to-reach population, the non-random nature of our study sample potentially limits the applicability of our findings to PWID with HIV in Vietnam who were not recruited.

**Generalizability**

Our study focused on an important population in the Vietnamese HIV epidemic, and findings may be relevant to other parts of Asia and Eastern Europe, where the HIV epidemic is concentrated among similar groups of men who inject drugs. Findings may be less relevant to other HIV populations, particularly the large, generalized epidemics of sub-Saharan Africa driven by sexual transmission. However, there is increasing relevance to the opioid epidemic in the US, as opioid users transition to injection drug use and engage in sharing behaviors. In addition, this study demonstrates a methodological approach that can be applied to other populations and settings to understand individual determinants of HIV transmission and their net contribution to ongoing infection.

**Public Health Implications and Future Directions**

Future research probing our mixed findings for the effect of depression on sharing injection equipment (but not condomless sex) and on ART initiation (but not viral

suppression) will inform the design and implementation of interventions for PWID. To shed light on the extent to which successful depression treatment could avert future infections, modeling work could simulate potential intervention scenarios that vary the coverage and efficacy of depression interventions designed to decrease depressive symptoms and subsequently lower sharing behaviors and viral load (as informed by this study). Depression treatment could be modeled alongside current interventions (ART, needle exchanges, methadone maintenance treatment [MMT]) to understand the optimal combination of these approaches in decreasing HIV incidence among PWID.

Addressing the high burden of depression among PWID through future intervention and treatment will improve the mental health of this population in addition to possible HIV prevention benefits. Current work in Vietnam is developing and implementing evidence-based interventions to facilitate the engagement of PWID in both HIV and substance use care (e.g., ClinicalTrials.gov NCT03952520). Incorporation of mental health services alongside HIV and substance use care is complementary and has the potential to further improve HIV and drug use-related outcomes. Specifically, incorporating depression screening and treatment into HIV and substance use care fits well with increasing prioritization and funding for depression in Vietnam in recent years.

To inform possible integration of depression, HIV, and substance use care, depression screening and treatment interventions could be piloted at ART or MMT clinics, providing an access point to PWID with possible comorbid depression and HIV. To reach PWID who are not already engaged in care, qualitative work among ART or MMT clients engaged in depression interventions could solicit input on recruitment strategies and determine the feasibility of ART or MMT clients as recruiters of PWID

outside of clinic settings (given the success of using current and former PWID as recruiters in this study's parent trial). Clinic-based interventions could consist of a brief screening tool (such as the CES-D), and for participants who screen positive for depressive symptoms, provision of evidence-based depression treatment (e.g., antidepressant medication prescribed alongside ART or MMT; cognitive behavioral therapy or problem solving therapy at clinic visits).

In conclusion, this dissertation study found some evidence that interventions to treat depression may decrease injection equipment sharing and improve ART uptake, lowering the corresponding risk of HIV transmission among PWID. Screening and treating depressive symptoms among PWID presents an opportunity not only to benefit mental health but also to reduce the harms of drug abuse and improve HIV outcomes in this vulnerable population.

# APPENDIX

**Appendix 1. R packages used in analyses.**
Source: CRAN package repository https://cran.r-project.org/

| Package Name | Version |
|---|---|
| binom | 1.1-1 |
| boot | 1.3-20 |
| broom | 0.4.3 |
| cmprsk | 2.2-7 |
| contrast | 0.21 |
| cowplot | 0.9.3 |
| dagitty | 0.2-2 |
| datapasta | 3.0.0 |
| datasets | 3.4.3 |
| doMC | 1.3.5 |
| dplyr | 0.8.3 |
| forcats | 0.3.0 |
| foreach | 1.4.4 |
| foreign | 0.8-69 |
| Formula | 1.2-2 |
| geepack | 1.2-1 |
| gganimate | 1.0.4 |
| ggbeeswarm | 0.6.0 |
| ggdag | 0.1.0 |
| ggfortify | 0.4.5 |
| ggplot2 | 3.2.1 |
| gifski | 0.8.6 |
| glmnet | 2.0-16 |
| glue | 1.3.1 |
| graphics | 3.4.3 |
| grDevices | 3.4.3 |
| haven | 2.1.1 |
| Hmisc | 4.1-1 |
| knitr | 1.24 |
| lubridate | 1.7.4 |
| magrittr | 1.5 |
| markdown | 0.8 |
| methods | 3.4.3 |
| mgcv | 1.8-22 |
| mice | 3.3.0 |
| networkD3 | 0.4 |
| plotly | 4.8.0 |
| plotROC | 2.2.1 |
| polynom | 1.3-9 |

| | |
|---|---|
| prettyunits | 1.0.2 |
| psych | 1.7.8 |
| purrr | 0.3.3 |
| RColorBrewer | 1.1-2 |
| readr | 1.3.1 |
| readxl | 1.0.0 |
| rlang | 0.4.0 |
| rmarkdown | 1.15 |
| scales | 1.0.0 |
| shiny | 1.1.0 |
| sourcetools | 0.1.6 |
| splines | 3.4.3 |
| stats | 3.4.3 |
| stringr | 1.4.0 |
| survival | 2.41-3 |
| survminer | 0.4.3 |
| survutils | 1.0.2 |
| tableone | 0.9.2 |
| tibble | 2.1.3 |
| tidyr | 1.0.0 |
| tidyverse | 1.2.1 |
| utils | 3.4.3 |
| VIM | 4.8.0 |
| visreg | 2.5-0 |

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