

UNDERSTANDING HIV-RELATED STIGMA AND ART ADHERENCE AMONG  
ADOLESCENTS AND YOUNG ADULTS LIVING WITH HIV IN SOUTH AFRICA  
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## ABSTRACT

**Background.** Adherence to antiretroviral therapy (ART) is necessary to achieve and maintain HIV viral suppression, and stigma is a known risk factor for poor adherence among adults. However, research on sustained HIV care engagement has historically overlooked adolescents despite emerging evidence that they have worse treatment outcomes than adults. This thesis consists of three studies focused on understanding factors associated with suboptimal antiretroviral therapy (ART) adherence and HIV-related stigma among adolescents and young adults living with HIV in South Africa. The aims are to increase understanding of the risk factors associated with HIV-related mistreatment, elucidate the pathway from HIV-related mistreatment to ART adherence, and identify co-occurring barriers to adolescent ART self-management.

**Methods.** The studies used cross-sectional survey data from a program evaluation conducted in two high HIV-prevalence provinces of South Africa with 1,273 youth living with HIV, aged 14-24, and enrolled in peer support groups led by community-based organizations serving orphans and vulnerable children. Statistical analysis included mixed effects logistic regression, path analysis and latent class analysis.

**Results.** The first study found that knowledge of HIV status by a friend, teacher, or sexual partner was significantly associated with increased adjusted odds of HIV-related mistreatment. The second study found that experiences of HIV-related mistreatment and anxiety were associated with decreased adjusted odds of reporting 90% past month ART adherence, while HIV-related shame and anxiety mediated the relationship between HIV-related mistreatment and ART adherence. The third study identified three distinct latent classes of individual-level barriers to daily ART among adolescents and young adults. Membership in the class reporting multiple reasons for missing doses, including concerns about side effects and treatment efficacy, was associated with lower adjusted odds of reporting 90% or higher past month ART adherence relative to the class that reported only missing doses due to forgetting or others being around.

**Conclusion.** Findings contribute to the nascent quantitative evidence base for modifiable risk factors associated with HIV-related stigma and ART adherence among vulnerable youth in South Africa. Addressing psychological well-being, including anxiety and disclosure concerns, may reduce experiences of HIV-related mistreatment and improve ART adherence.

## ACRONYM LIST

<b>AIDS</b>	Acquired Immune Deficiency Syndrome
<b>ALHIV</b>	Adolescents living with HIV
<b>ART</b>	Antiretroviral Therapy
<b>CINDI</b>	Children in Distress Network (Organisation)
<b>FHI360</b>	Family Health International 360 (Organisation)
<b>GoSA</b>	Government of South Africa
<b>HIV</b>	Human Immunodeficiency Virus
<b>HIVSA</b>	HIV South Africa (Organisation)
<b>LMIC</b>	Low or middle-income country
<b>NSP</b>	National Strategic Plan
<b>OVCA&amp;Y</b>	Orphaned and Vulnerable Children, Adolescents and Youth
<b>PEPFAR</b>	The United States President's Emergency Plan for AIDS Relief
<b>PHVP</b>	Preventing HIV/AIDS in Vulnerable Populations Project
<b>SSA</b>	Sub-Saharan Africa
<b>STI</b>	Sexually Transmitted Infections
<b>TLD</b>	Fixed-dose combination [FDC] of tenofovir [TDF] 300 mg + lamivudine [3TC] 300mg + dolutegravir [DTG] 50 mg)
<b>UNAIDS</b>	Joint United Nations Programme on HIV/AIDS
<b>USAID</b>	United States Agency for International Development
<b>UTT</b>	Universal test and treat
<b>VLS</b>	Viral load suppression
<b>WHO</b>	World Health Organization

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## BACKGROUND AND SIGNIFICANCE

### THE HUMAN IMMUNODEFICIENCY VIRUS (HIV) AND ANTIRETROVIRAL THERAPY (ART)

The Human Immunodeficiency Virus (HIV) is a retrovirus that causes acquired immune deficiency syndrome (AIDS), which is defined by characteristic infectious or oncological complications (Deeks, Overbaugh, Phillips, & Buchbinder, 2015). HIV transmission may occur when infected body fluids contact mucosal tissue, blood or broken skin, which may arise sexually, parenterally or perinatally (Deeks et al., 2015). The infection is persistent, progressive and almost always fatal when untreated due to pervasive immune dysfunction and dysregulation, leading to an increased likelihood of disease (Moir, Chun, & Fauci, 2011). HIV infection is also characterized by a high rate of viral mutation and variation, which can lead to the development of drug resistance (Overbaugh & Bangham, 2001). However, combination antiretroviral therapy (ART) is highly effective at suppressing viral replication and allowing for immune recovery, reduced risk of AIDS, prevention of viral evolution and drug-resistance, and the near elimination of transmission risk (Deeks et al., 2015). Global guidelines recommend initiating ART immediately or within days of HIV diagnosis (WHO, 2016), given the benefits of early ART initiation across populations (Danel et al., 2015; Lundgren et al., 2015; Schomaker et al., 2017; Shiao et al., 2017; Violari et al., 2008). In addition, long-term adherence to ART is required to maintain viral suppression (Bangsberg et al., 2001; Davey et al., 1999; Gavin & Yogeve, 2002; Gibb et al., 2003).

## HIV AND AIDS IN SOUTH AFRICA

### THE BURDEN OF DISEASE AMONG YOUTH

South Africa has the largest number of people living with HIV, globally (UNAIDS, 2022a). Based on UNAIDS estimates, 7.5 million people were living with HIV in 2021 in South Africa, which is close to one in five persons (UNAIDS, 2022a). The HIV epidemic is generalized and high-prevalence, with significant age, sex, and regional differences (Simbayi, Zuma, Zungu, & al, 2019). Despite declines in HIV incidence and AIDS-related deaths in the general population since 2010, the incidence rate remains high at 7.79 per 1000 people (UNAIDS, 2021a). Over one-third of all new HIV diagnoses are among youth aged 15 to 24 years, with the incidence among females three times that of males in this age group (Simbayi et al., 2019). In addition, almost 4% of adolescents in South Africa are living with HIV (Zungu et al., 2020), with prevalence estimated between 15-19% among females ages 20-24 (NDoH, Stats SA, SAMRC, & ICF, 2019; Simbayi et al., 2019).

### HIV TREATMENT CASCADE & STIGMA

The HIV treatment cascade is a cross-sectional, population-level representation of the stages of HIV care, which may include diagnosis, linkage to care, retention in care, adherence to ART, and viral load suppression (VLS) (Kay, Batey, & Mugavero, 2016). The Joint United Nations Programme on HIV/AIDS (UNAIDS) scaled up ‘fast-track’ global treatment targets for this cascade in 2015: By 2030, 95% of people living with HIV know their status, 95% of people living with HIV who know their status initiate treatment, and 95% of people living with HIV on treatment are virally suppressed (UNAIDS, 2015).



To realize these targets, timely HIV diagnosis, linkage to and retention in HIV care and support programs are necessary (UNAIDS, 2021b).

A 2017 nationally representative cross-sectional survey estimated that among persons ages 15-64 in South Africa, 85% of people living with HIV know their status, and 71% of these persons are on ART, of which 87% are virally suppressed (Simbayi et al., 2019). In contrast, adolescents have lower attainment of each step of the treatment cascade: 62% of adolescents living with HIV aged 10-19 know their status, and 65% of those who know their status are on ART, of which 78% are virally suppressed (Zungu et al., 2020). A systematic review of observational cohort studies in South Africa directly comparing adolescents or young adults to older adults has similarly found lower rates of retention in care and VLS among youth (Zanoni, Archary, Buchan, Katz, & Haberer, 2016). These results are consistent with research elsewhere in Sub-Saharan Africa (Auld et al., 2014; Grimsrud et al., 2014; Havlir et al., 2020; Nachega et al., 2009; Slogrove & Sohn, 2018).

To meet the 2030 treatment targets, the current (2021-2026) UNAIDS global strategy to end AIDS also emphasizes addressing the structural drivers and inequalities that impede service access and delivery, especially stigma and discrimination (UNAIDS, 2021b).

HIV-associated stigma is prevalent in South Africa (Chan, Tsai, & Siedner, 2015; Stangl et al., 2020), including among youth people (UNICEF, 2022c). For example, in a nationally representative survey conducted in 2017, 21.5% of females and 25.2% of males aged 15-19 had discriminatory attitudes towards people living with HIV<sup>1</sup>

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<sup>1</sup> The SABBSM 2017 measured the number of people who answered no to either of the following two questions: 1) Would you buy fresh vegetables from a shopkeeper or vendor if you knew that this person

(UNICEF, 2022c). When stigma is applied to people living with or associated with HIV, it manifests in a range of individual-level experiences, such as anticipated, internalized and enacted stigma (Earnshaw & Chaudoir, 2009). These experiences of stigma by people living with HIV, alongside the beliefs, attitudes and actions of people not living with HIV, impede access to, uptake of and retention in HIV care and result in poor physical and mental health (UNAIDS, 2020a).

## SIGNIFICANCE

The present generation of young people is the largest in human history<sup>2</sup>, and their current health and well-being have significant consequences for their adult health and the children they may parent (Patton et al., 2018). The global burden of mortality in young people (aged 10-24) is shifting to Sub-Saharan Africa (SSA) due to a combination of population growth in this age group alongside worse mortality outcomes (Ward et al., 2021). Indeed, globally, almost one-third of deaths in young people occur in SSA, where HIV is a leading cause of death among females in all adolescent age groups (Ward et al., 2021). Lower testing coverage, ART initiation, treatment retention and adherence rates in South Africa and elsewhere in sub-Saharan Africa may explain the increase in AIDS-related deaths among adolescents between 2005 and 2015, a time when mortality decreased in all other age

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had HIV? 2) Do you think children living with HIV should be able to attend school with children who are HIV negative?

<sup>2</sup> As of 2021, there were 1.85 billion young people between the ages of 10-24 according to the United Nations Population Fund (UNPF) State of the World's Population Report (SoWP) demographic indicators (UNFPA, 2021). This is an increase from the 1.8 billion cited as the largest cohort of young people in the history of the world in the 2014 SoWP report, which focused on the potential demographic dividends of protecting and investing in this population (UNFPA, 2014).

groups<sup>3</sup> (Adejumo, Malee, Ryscavage, Hunter, & Taiwo, 2015). In recognition of the critical lack of investment to date in adolescent health, the World Health Organization issued a call in 2017 for accelerated action for the health of adolescents, including increased research on how best to support them (WHO, 2017a).

Adolescents and young adults have poor outcomes along the HIV treatment cascade relative to the 95-95-95 treatment targets, yet research on this population is limited (Armstrong et al., 2018a; Ridgeway et al., 2018). A global adolescent health research priority-setting exercise emphasized identifying factors that facilitate HIV treatment uptake, retention, and adherence and minimize treatment failure among adolescents (Hindin, Christiansen, & Ferguson, 2013). Research on sustained HIV care engagement and ART adherence among overlooked populations, including adolescents and males, was identified as critical for implementing the WHO's Universal Test & Treat approach (UTT) approach (Yotebieng et al., 2019). In addition, a global research agenda focused on operational research for adolescents living with HIV suggested that effective monitoring approaches are needed to improve adherence and retention in care (Armstrong et al., 2018a).

Research on engagement in HIV care, including ART adherence, among young people in SSA has been mainly qualitative or cross-sectional (Adejumo et al., 2015; Ammon, Mason, & Corkery, 2018; Hudelson & Cluver, 2015). Further, most research has focused on

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<sup>3</sup> UNAIDS estimates indicate adolescents ages 10-19 are the only age group in which AIDS-related deaths are not decreasing. Between 2005 and 2015, there was a 45% increase in AIDS-related deaths among adolescents age 15–19 (UNAIDS, 2016)

adolescents with perinatally acquired HIV (Adejumo et al., 2015; Ammon et al., 2018; Hudelson & Cluver, 2015). While several reviews published in recent years focused on ART adherence among children and adolescents (Adejumo et al., 2015; Ammon et al., 2018; Hudelson & Cluver, 2015; Kim, Gerver, Fidler, & Ward, 2014), relatively few studies have included young adults (age 20-24) (Kim et al., 2014), despite the high incidence and prevalence of HIV in this age group. Outside of high-income countries, few quantitative studies have explored factors related to the social environment, such as stigma, as correlates or predictors of adolescent ART adherence (Adejumo et al., 2015; Hudelson & Cluver, 2015). Many studies also lack information on factors that may confound adherence, such as sociodemographic status (Kim et al., 2014). Finally, most large-scale research efforts among adolescents living with HIV in low and middle-income countries recruit youth from public ART clinics (Cluver, Toska, Hodes, et al., 2019; Ssewamala et al., 2019), which limits the generalizability of findings.

This thesis presents the results of several studies designed to increase understanding of the risk factors associated with experiences of HIV-related stigma, elucidate the pathway from HIV-related stigma to ART adherence, and identify barriers to adolescent ART self-management. Data comes from a large sample of adolescents (aged 10-19) and young adults (aged 20-24) living with HIV and recruited from community-based organizations in two high-prevalence provinces, KwaZulu-Natal and Gauteng, of South Africa. Findings from these studies contribute to the nascent quantitative evidence base for modifiable risk factors associated with HIV stigma and ART adherence among vulnerable youth.

## LITERATURE REVIEW

### THEORETICAL BASIS FOR INVESTIGATION

#### THE BIOECOLOGICAL MODEL OF HUMAN DEVELOPMENT

The bioecological model of human development (Bronfenbrenner, 2005; Bronfenbrenner & Ceci, 1994) provides this investigation's theoretical basis. The bioecological model builds on Bronfenbrenner's oft-cited ecological systems theory (Bronfenbrenner, 1979) to balance context, development, and the interaction between the two. In other words, it ensures attention not only to the influence of the environment (i.e., context, a series of nested and interacting ecological systems) but also to the development (biopsychological characteristics) of the individual (Derksen, 2010). Furthermore, Bronfenbrenner emphasizes 'proximal processes' to describe the progressive and reciprocal interactions between an individual and the persons, objects, and symbols of their immediate environment (Bronfenbrenner & Ceci, 1994). These processes are a joint function of the characteristics of the individual, the immediate and remote environment, the developmental outcomes of interest, and the social reality over time (Bronfenbrenner & Ceci, 1994). The following section discusses adolescent HIV-related outcomes in the context of the bioecological model.

#### ADOLESCENT DEVELOPMENT IN CONTEXT

##### PERSON: CHARACTERISTICS OF ADOLESCENCE

While unique physiological changes are associated with chronological age, including sexual maturation during adolescence, developmental life stages are also social constructs

(Linders, 2017). As such, accepting specific behaviors or conditions as ‘normal’ during adolescence may mask the social, economic and political structures that give rise to and reinforce these behaviors in the first place (Linders, 2017). For example, the social and cultural values that view adolescent sex as inappropriate and perilous are reinforced by laws prohibiting or impeding teenagers from independently accessing the sexual and reproductive health services that could reduce their risk. What determines the acceptability of behavior during a life stage and how behavior is subsequently regulated differs in every context (Linders, 2017). Additionally, what is considered acceptable behavior is filtered through other social identities, including class, gender, race, and sexual orientation (Linders, 2017). Furthermore, the construct of development is culturally conditioned, yet most developmental research comes from Western contexts, suggesting expectations around normative adolescent development are biased toward middle-class European American children (Lansford, French, & Gauvain, 2021).

Nonetheless, adolescence is typically characterized by the onset of puberty and sexual maturity, which involve dramatic physical and psychosocial changes. Notable changes include the growing capacity to think abstractly; changing environments and the increasing influence of peers; behavioral experimentation and risk-taking; and the development of an independent identity (Woolfolk & Perry, 2015). As a result, peer and community networks grow in importance as adolescents move away from primarily family-based relationships (Zungu et al., 2020). However, supportive family relationships are still meaningful, especially in handling difficult situations (Zungu et al., 2020). Decision-making may be driven by social approval, conformity, and an evolving self-concept, including personal

beliefs, values, and standards (Zungu et al., 2020). Youth face peer pressure and concerns about stigma, the emergence of risk behaviors such as alcohol, substance, and tobacco use, and the increasing prevalence of other mental and physical comorbidities (Petersen, Qualter, & Humphrey, 2019; Snow, Sismanidis, Denholm, Sawyer, & Graham, 2018; WHO, 2018). Due to the extent of physical, emotional, and social changes they experience, adolescents may be especially vulnerable to mental and behavioral health disorders (WHO, 2017b).

### PROCESSES: MANAGING HIV IN SOUTH AFRICA

Adherence is a multi-faceted health behavior that refers to how much a person's behavior coincides with medical or health advice (Modi et al., 2012). ART adherence typically refers to taking a medication regimen at prescribed times and may be compromised by missed or late doses, treatment interruption or discontinuation, or subtherapeutic dosing (Vreeman et al., 2014). Adherence behaviors are influenced by multiple factors, including ART regimen and administration, short-term and long-term toxicities of ART, the person's developmental stage and psychosocial, behavioral, and sociodemographic characteristics, as well as contextual factors related to the health system, political and economic conditions, and social norms (Ammon et al., 2018; Hudelson & Cluver, 2015; Kim et al., 2014; Langebeek et al., 2014; Shubber et al., 2016).

In-depth qualitative research from South Africa suggests that adolescents primarily view ART as a reminder of their HIV and how they differ from family and friends, with the rigor around adherence contrasting with the carefree, fun lifestyle they aspire to (S. Madiba &

Mokgatle, 2016; Zungu et al., 2020). Furthermore, the desire to be considered ‘normal’ by peers may also lead to rebellion against healthcare workers or caregivers (Zungu et al., 2020). In turn, healthcare workers and caregivers of HIV-positive adolescents consider non-adherence a form of disobedience, resulting in support tactics involving reprimand, punishment, surveillance, instruction, and information-giving (Zungu et al., 2020). As a result, adolescents may consider adherence to be a practice of deference to the authority of elders (e.g., caregivers or healthcare workers) and question the biomechanics and efficacy of treatment. Experimentation with missed doses is thus common, especially among older adolescents (Loveday, Furin, Hlangu, Mthethwa, & Naidoo, 2022; Zungu et al., 2020).

In addition to facing a life-threatening and chronic disease, adolescents living with HIV who know their status must manage the implications of a stigmatizing disease while navigating expanding peer networks and intimate relationships. Adolescents living with HIV may grieve the loss of a normal life and feel isolated from their peers due to their diagnosis (Zungu et al., 2020). Moreover, concerns around stigma and discrimination may prevent adolescents from disclosing their HIV status outside the home (Loveday et al., 2022; S. Madiba & Mokgatle, 2016), limiting available support and increasing vulnerability to mental health disorders (Sweeney & Venable, 2016). Indeed, depression is a risk factor for poor ART adherence among youth across income settings (Haas et al., 2023; Haas et al., 2020; Vreeman, McCoy, & Lee, 2017), and depression is consistently linked with HIV-related stigma (Logie & Gadalla, 2009; Sweeney & Venable, 2016; Turan et al., 2016).



Adolescents may also experience unstable living environments and lack the support of parents in navigating challenges due to the high rate of orphanhood among this population in South Africa (Loveday et al., 2022; Zungu et al., 2020). Further, adolescents may be expected to assume responsibility for their medication management, which may be unrealistic due to complicated regimens and demanding schedules (Hazra, Siberry, & Mofenson, 2010; Loveday et al., 2022). The adverse effects of living in poverty, including competing priorities for survival and the unpredictability of life events, alongside social and gender norms that affect one's social identity, also interfere with engagement in HIV care (Eshun-Wilson, Rohwer, Hendricks, Oliver, & Garner, 2019). Challenges accessing appropriate healthcare are common, including economic barriers and healthcare services focused solely on pediatric and adult populations (Fatti, Shaikh, Eley, & Grimwood, 2014; Ferrand et al., 2009). Further, interactions with the health system, often described as punishing and uninviting, may alienate some patients while providing structure for others (Eshun-Wilson et al., 2019).

On the other hand, positive external influences, including logistic, emotional, or financial support from the household, community, or healthcare facility, may improve retention in care and treatment adherence (Eshun-Wilson et al., 2019). These external factors, alongside personal motivators, lead to a "tipping point" in time when patients choose to either engage or disengage from care, and people may move in and out of these care states in response to fluctuations in influences over time (Eshun-Wilson et al., 2019).

## SOCIOHISTORICAL CONTEXT

Bronfenbrenner's model includes an additional element, the chronosystem, or historical time, encompassing the whole ecological system (Lansford et al., 2021).

South Africa's legacy of race- and sex-based discrimination, especially as codified by the state policy of apartheid (1948-1994), permeates all aspects of health and the health system (Coovadia, Jewkes, Barron, Sanders, & McIntyre, 2009; Mabaso et al., 2019) within which adolescents manage their care. Racial, provincial and gender inequities in health are apparent, with substantially different rates of disease and mortality reflecting differences in access to basic household living conditions and other determinants of health (Coovadia et al., 2009). The historical roots of the determinants of health in South Africa are especially obvious in the HIV and tuberculosis epidemics, which disproportionately affect the Black African population<sup>4</sup> (Abdool Karim, Churchyard, Karim, & Lawn, 2009). Black Africans have a significantly higher prevalence of HIV compared to other races in South Africa (Mabaso et al., 2019). Among adolescents living with HIV, ninety-five percent are Black African, with the remaining 3.4% White and 1.2% Colored (Zungu et al., 2020).

Income inequality, specifically the impoverishment of Black Africans alongside general White affluence, has an outsize influence on health outcomes, including the high burden of poverty-related diseases, crime and violence (Coovadia et al., 2009). Wealth disparities increased following democracy (Coovadia et al., 2009), with the most recent

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<sup>4</sup> Racial categories are those used by the national census (and in common use in South Africa) and do not imply acceptance of racial attributes.

Gini coefficient<sup>5</sup> estimated as 63 in 2014 (World Bank, 2021). However, the national system of social grants, including the Child Support Grant, has narrowed income disparities somewhat despite macroeconomic policy focused on growth over redistribution (Coovadia et al., 2009). Severely constrained government expenditures on health and social services in the 1990s also affected wealth distribution, though efforts were made to improve access to essential services such as water and electricity (Coovadia et al., 2009). Further, the deliberate under-education and menial employment of non-White populations historically are evident in current low educational attainment, a dysfunctional education system and persisting high unemployment rates (Coovadia et al., 2009), which further impact socioeconomic well-being.

The delayed rollout of ART has also profoundly affected the current HIV epidemic in South Africa, resulting in a high rate of preventable morbidity, mortality, orphanhood and vertical transmission of HIV. Most notably, the post-Apartheid government of Thabo Mbeki, influenced by AIDS denialism, acted as an obstacle to the early roll-out of ART (Chigwedere, Seage, Gruskin, Lee, & Essex, 2008). As a result, perinatal transmission prevalence was as high as 26.5% in 2000, though now reduced to under 3% nationally (Burton, Giddy, & Stinson, 2015; Wessels et al., 2020). Modeling estimates suggest the provision of ART between 2000 and 2005 could have prevented 330,000 deaths and 35,000 perinatal transmission events (Chigwedere et al., 2008). With ART access and treatment improvements, many infants with vertically acquired HIV have reached adolescence (Idele et al., 2014) but not without unique treatment considerations.

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<sup>5</sup> The Gini index measures the degree of income inequality (0 represents perfect equality, while 100 implies perfect inequality)

Children with perinatally-acquired HIV who reach adolescence are often heavily treatment-experienced with extensive drug resistance and morbidity due to the effects of long-term HIV disease and treatment (Hazra et al., 2010).

The estimated number of children (aged 0-17) orphaned due to AIDS in South Africa is estimated to be 1.6 million (UNAIDS, 2021a), and orphanhood is high among adolescents ages 10-19 living with HIV (43.7% were orphans as of 2017; 17.4% paternal; 13.4% maternal; 12.9% double) (Zungu et al., 2020). Orphans are more likely to be living with HIV than non-orphans due to vertical transmission (Kidman & Anglewicz, 2017) and exposure to a range of social vulnerabilities (Zungu et al., 2020). Higher levels of sexual risk behavior among orphaned youth than non-orphaned youth may also play a role (Operario, Underhill, Chuong, & Cluver, 2011). However, orphans' access to HIV services remains low, with maternal orphans experiencing delayed diagnosis and treatment compared to non-orphans (Mokgatle & Madiba, 2015). In addition, among those living with HIV and retained in care for at least 12 months, orphans are more likely than non-orphans to have detectable viral loads (Hendrickson et al., 2019). Orphan status has also been associated with lower ART adherence and higher treatment interruption (Vreeman et al., 2019).

## HYPOTHESIS AND RESEARCH QUESTIONS

This research aims to elucidate factors associated with HIV-related stigma and ART adherence among adolescents and young adults living with HIV in South Africa. Findings can inform interventions to improve HIV treatment outcomes for this vulnerable population. The specific research questions and hypotheses are:

***Aim 1. Understand disclosure and experiences of HIV-related stigma among adolescents and young adults living with HIV in South Africa***

**Research question 1:** Does knowledge of one's HIV status outside of the family (teacher, friend, sexual partner) and factors that may inadvertently disclose an adolescent's HIV status (poor health, missed school) increase the odds of recent experiences of HIV-related discrimination, controlling for age, sex and socioeconomic status (food insecurity, housing type)?

**Hypothesis 1:** Adolescents who report factors associated with inadvertent disclosure and disclosure to non-family members will have higher odds of HIV-related discrimination than adolescents who do not report factors associated with inadvertent disclosure or disclosure to non-family members.

***Aim 2. Explore pathways from HIV-related mistreatment and shame to suboptimal ART adherence among adolescents and young adults living with HIV in South Africa***

**Research question 2.1:** Are HIV-related discrimination and shame associated with increased odds for suboptimal ART adherence, controlling for age, sex,

socioeconomic status (food insecurity, housing quality) and psychological distress (depression, anxiety)?

**Hypothesis 2.1:** Adolescents who report recent experiences of HIV-related discrimination and HIV-related shame will have higher odds of suboptimal ART adherence than adolescents who do not report HIV-related discrimination or shame.

**Research question 2.2:** Do HIV-related shame and psychological distress (depression, anxiety) mediate the relationship between HIV-related discrimination and suboptimal ART adherence?

**Hypothesis 2.2:** HIV-related shame and psychological distress will partially mediate the relationship between HIV-related discrimination and suboptimal ART adherence. In other words, there will be a direct effect of HIV-related discrimination on suboptimal ART adherence and an indirect effect via HIV-related shame, depression and anxiety.

***Aim 3. Conduct latent class analysis of barriers to daily ART among adolescents and young adults living with HIV in South Africa***

**Research question 3.1:** Are there distinct subgroups (classes) of adolescents and young adults living with HIV and currently on ART that report similar patterns of reason/s for missing ART doses? If so, what is the distribution of adolescents across these subgroups?

**Hypothesis 3.1:** Within this sample of adolescents and young adults on ART, there will be classes with distinct and different patterns of reasons for missed ART.

**Research question 3.2:** Are sociodemographic characteristics (age, sex, socioeconomic status) associated with sub-group membership?

**Hypothesis 3.2:** Demographic characteristics associated with developmental maturity (e.g., age) will be associated with class membership.

**Research question 3.3:** Is membership in each subgroup associated with past-month suboptimal ART adherence, controlling for significant sociodemographic characteristics and health access (distance to the clinic) and familial support (accompaniment, reminders) factors?

**Hypothesis 3.3:** Classes endorsing multiple reasons for missed ART will be associated with past-month ART non-adherence.

## METHODS AND MATERIALS

### SETTING: SOUTH AFRICA

The government of South Africa (GoSA)'s approach to HIV epidemic control is guided by the 2017-2022 South Africa National Strategic Plan for HIV, TB, and Sexually Transmitted Infections (NSP) (SANAC, 2017). The NSP focuses strategically on 27 high-burden districts and prioritizes adolescents and young adults, among other key populations. In addition, the GoSA is supported by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), which is the US government's global response to the HIV epidemic. PEPFAR SA works with the GoSA toward the goal of HIV epidemic control by providing substantial and targeted support to facility- and community-based settings to close the treatment gap.

South Africa has national HIV policies aligned with global recommendations (NDoH, 2016), including The WHO's 'treat all' approach, making ART eligible regardless of CD4 count (WHO, 2016). Currently, the approved first-line regimen for all eligible adults, adolescents, and children over the age of 10 years and weighing at least 20 kg is TLD (defined as a fixed-dose combination [FDC] of tenofovir [TDF] 300 mg + lamivudine [3TC] 300mg + dolutegravir [DTG] 50 mg) (NDoH, 2020). In addition, South Africa has the largest public antiretroviral treatment (ART) program globally, which has significantly reduced HIV-associated morbidity and mortality rates since its inception (Maartens, 2014). The program includes free ART, laboratory testing, doctor consultations, management of opportunistic infections and ART side-effects, counseling, nutritional advice, and support.



## DATA INTEGRATION TO IMPROVE YOUTH OUTCOMES STUDY (ALHIV STUDY)

The study design for this dissertation is a secondary analysis of cross-sectional survey data acquired from the baseline round of the *Data integration to improve youth outcomes* study (ALHIV study). The ALHIV baseline survey was conducted from June 2019-March 2020. The study was designed to understand the potential effects of a peer support group on ART initiation and adherence, sexual risk-taking, and psychological wellbeing outcomes among youth beneficiaries (age 14-24) living with HIV.

### STUDY POPULATION & SAMPLING APPROACH

In South Africa, PEPFAR funds The U.S. Agency for International Development South Africa's (USAID/SA) community-based program, *Preventing HIV/AIDS in Vulnerable Populations* (PHVP) project. This five-year (2018-2023) project is implemented in collaboration with the GoSA (Hasha, 2017). PHVP includes support for the Orphans and Vulnerable Children, Adolescents and Youth (OVCA&Y) comprehensive case management program, among other activities designed to accelerate and sustain HIV epidemic control in South Africa. In addition, the project makes a concerted effort to identify children living with HIV or at risk of acquiring HIV, enroll them in HIV care and treatment, and support their retention in those services. The OVCA&Y program operates within nine of the 27 high-burden districts prioritized by GoSA (Hasha, 2017). The most extensive OVCA&Y programs are in KwaZulu-Natal and Gauteng, where most of South Africa's HIV-positive adolescents live (27% and 19%, respectively, of all adolescents living with HIV aged 10-19) (Zungu et al., 2020).

Three South African non-profit organizations funded under the PHVP project (CINDI, FHI 360, and HIVSA) were responsible for recruiting adolescents and young adults living with HIV for participation in a structured peer support group (Vhutshilo 3) from program sites in KwaZulu-Natal and Gauteng provinces beginning in early 2019.

Vhutshilo 3 is designed to provide adolescents living with HIV with prevention and treatment education, skills, and support to address mental health. The intervention consists of 14 one-hour sessions by trained adult facilitators in groups of 15-20 ALHIV. All beneficiaries considered for enrolment in Vhutshilo 3 were assessed for eligibility by program partners using data recorded on standardized case management forms. Vhutshilo 3 eligibility criteria include age 14-24, awareness of their HIV-positive status, and willingness to participate in the intervention. All adolescent and young adult subjects were expected to read and write in English as the language of the intervention instruction and an expectation of intervention enrolment.

A convenience sampling approach was used. Only sites with experience serving youth living with HIV and conducting structured interventions were eligible for inclusion in the sample. All groups commencing between June 2019 and March 2020 within each eligible site were invited to participate in the baseline survey for a total of 128 Vhutshilo 3 groups at 38 sites. Assent was obtained for 1,451 participants among the 1,753 beneficiaries present on the survey day, yielding a response rate of 83%.

## ETHICAL CONSIDERATIONS, DATA COLLECTION PROCEDURES & ANALYSIS

As human subjects research, this study was reviewed and approved by the Pharma Ethics Research Ethics Committee in South Africa and the Tulane University Institutional Review Board in the United States. Voluntary informed consent for survey participation was sought for all participants; the Tulane institutional and local review boards granted a waiver of parental permission for adolescents under 18. Participation in the survey did not affect intervention receipt.

Among consenting/assenting youth, a one-hour survey was administered in English by trained research staff to each Vhutshilo 3 group. The research staff read each question aloud to the group, and participants self-reported their answers in writing on a pre-printed questionnaire. Participants were seated at a sufficient distance from each other to ensure the confidentiality of the data. Confidentiality was also maintained by using coded identifiers, and the participant sealed each completed questionnaire in an individual envelope before returning it to the research staff. Upon completing the survey, participants received refreshments and a small monetary reimbursement for their time (ZAR 20, approximately US\$1.20).

After reviewing the survey data, 64 survey records were excluded due to age discrepancies between survey and program records (suggesting ineligibility), and 114 were excluded because the youth denied their HIV status was positive (e.g., wrote "HIV-negative" on the survey or refused to answer any of the 11 questions related to HIV status). Thus, the final baseline survey dataset comprised 1,273 individual-level records (survey responses).

## MAIN RESULTS

### PAPER 1. DISCLOSURE AND EXPERIENCES OF HIV-RELATED STIGMA AMONG ADOLESCENTS AND YOUNG ADULTS LIVING WITH HIV IN SOUTH AFRICA

#### INTRODUCTION

Stigma and related discrimination are a significant impediment to achieving the UNAIDS 95-95-95 treatment goals, and addressing their effects is at the forefront of global HIV epidemic control efforts (UNAIDS, 2020b). Improved HIV survival and widespread stigma reduction campaigns have helped diminish (Chan et al., 2015; Stangl et al., 2020), but not erase, historically stigmatizing attitudes toward people living with HIV in sub-Saharan Africa (Adejumo et al., 2015). Among young people living with HIV in South Africa, HIV-related stigma has been linked to reduced retention in HIV care (Pantelic, Casale, Cluver, Toska, & Moshabela, 2020) and lower ART adherence (Loveday et al., 2022).

Stigma is a multidimensional construct involving the social devaluation of a person based on an attribute associated with negative public attitudes (Goffman, 1963). One of the many HIV-related stigma dimensions at the individual level is *enacted* stigma, the direct experience of devaluation, discrimination, or mistreatment based on one's HIV status (Earnshaw & Chaudoir, 2009). An experience of enacted stigma is typically predicated

on external awareness of one's serostatus and is intimately linked to disclosure (Christopoulos et al., 2020). Nondisclosure has been hypothesized as a manifestation of anticipated or perceived stigma and linked to poorer ART adherence through lack of social support (Turan, Hatcher, et al., 2017) and concealment of status (Katz et al., 2013). On the one hand, limiting disclosure may restrict available support networks for managing HIV care, while disclosure, voluntary or otherwise, may increase the risk of discrimination and mistreatment (Turan, Hatcher, et al., 2017). Common disclosure concerns of youth include stigma, discrimination, rejection, unauthorized disclosure of their status and questions regarding how HIV was acquired (Thoth, 2014).

Adolescents are also concerned with inadvertent, accidental, or deductive disclosure of their status. Secrecy and concealment of status are commonly cited barriers to ART adherence among sub-Saharan youth (Ammon et al., 2018). Indeed, a reported concern among South African youth living with HIV is that friends or school members may notice the frequent absences from school necessary for clinic visits (Loveday et al., 2022; Maskew et al., 2016), which is in turn associated with reduced retention in care (Maskew et al., 2016). Physical appearances, such as weight loss or exhibiting symptoms or disabilities associated with HIV or AIDS, have also been linked to fear of unintentional HIV status disclosure in qualitative research (Lambert, Orrell, Bangsberg, & Haberer, 2018; Wolf et al., 2014).

Despite stigma's role in hindering optimal HIV care and treatment outcomes (UNAIDS, 2020b), few quantitative studies have explored the factors associated with specific

dimensions of stigma among adolescents and young adults living with HIV in sub-Saharan Africa. Available studies' findings on disclosure and stigma are mixed (Mugo et al., 2021; Nöstlinger, Bakeera-Kitaka, Buyze, Loos, & Buvé, 2015). For example, a survey among ninety-six 14-24-year-olds in Kenya found that participants who reported any self-disclosure were more likely to report enacted stigma than those with no self-disclosure (Mugo et al., 2021). In addition, respondents reported a higher prevalence of self-disclosure to family members than to other persons and disclosure to family was associated more strongly with experienced stigma than disclosure to non-family (Mugo et al., 2021). Another study among adolescents living with HIV aged 13-17 in Kenya and Uganda examined factors associated with self-disclosure to peers, including perceived stigma, and found no independent association (Nöstlinger et al., 2015). Finally, a study among adolescents living with HIV in Eastern Cape, South Africa, found a direct association between HIV-related disability, which may result in deductive disclosure, and enacted stigma (Pantelic, Boyes, Cluver, & Meinck, 2017).

The purpose of this study is to explore whether HIV status disclosure outside the household and factors that may inadvertently disclose an adolescent's status, such as poor health and missed school, are associated with recent experiences of HIV-related mistreatment (i.e., enacted stigma) in a large sample of South African youth living with HIV.

## METHODS

### STUDY DESIGN AND POPULATION

A cross-sectional survey was conducted from June 2019-March 2020 with participants of a structured support group intervention (Vhutshilo 3) provided by community-based organizations serving orphans and vulnerable children and youth (OVCY). Support group eligibility criteria included youth aged 14-24, living with HIV and aware of their status, and willing to participate in the intervention. Program recruitment occurred separately from study recruitment. All OVCY program sites in urban communities of Gauteng and KwaZulu-Natal provinces with experience serving youth living with HIV and conducting structured interventions were eligible for inclusion in the study (n=38 sites). Within each eligible site, all support groups which commenced operation between June 2019 and March 2020 were invited to participate in the baseline survey (n=128 groups).

### DATA COLLECTION PROCEDURES.

A one-hour survey was administered in English to each group at one of their initial Vhutshilo 3 sessions by trained staff from an external South Africa-based research organization. The research staff read each question aloud to the group, and participants self-reported their answers in writing using a printed questionnaire. The questionnaire included sociodemographic details, school attendance, physical health, which relationship types know the individual's HIV status, and experiences of HIV-related discrimination. Participant seating was spaced out to ensure the confidentiality of responses. Confidentiality was also maintained by using coded identifiers, and the participant sealed each completed questionnaire in an individual envelope before returning it to the research

staff. Upon completing the survey, participants received refreshments and a small monetary reimbursement for their time (ZAR 20, approximately US\$1.20).

## ETHICAL CONSIDERATIONS

The study was reviewed and approved by The Social Behavioral Institutional Review Board at Tulane University in the U.S. (study reference no: 2018-1736) and Pharma Ethics Independent Research Ethics Committee in South Africa (study reference no: 181021579). Written voluntary informed assent and consent for survey participation were sought for all participants; the Tulane and Pharma Ethics review boards granted a waiver of parental permission for adolescents under 18. Subjects who did not wish to participate in the survey were still encouraged to participate in the support group intervention.

## SURVEY MEASURES

### SOCIODEMOGRAPHIC CHARACTERISTICS.

Age, gender and socioeconomic status were included as control variables. Socioeconomic status was measured via questions on food insecurity and housing quality. Housing quality was measured by an affirmative response to three amenities: indoor plumbing, non-dirt-flooring, and electricity. Food security was assessed with one item from the Household Hunger Scale (Ballard, Coates, Swindale, & Deitchler, 2011) focused on missing a meal due to a lack of food in the household in the past week.

### DISCLOSURE.

A question on disclosure (*Do the following people know you are HIV-positive?* [e.g., caregiver, everyone in the household, any friend, any teacher/principal] was adapted from



a survey designed for adolescents living with HIV in the Eastern Cape of South Africa (Cluver, Toska, Hodes, et al., 2019). Response options were simplified to a dichotomous ‘yes/no’ response instead of the original seven levels of disclosure (Cluver, Toska, Wittesaele, Gutierrez, & Carlqvist, 2019). A second question limited to respondents who reported they had ever had sex asked: *The last time you had sex, did your partner know your HIV status? (Y/N)*. Responses to these questions were combined into one binary measure of ‘any’ disclosure to non-family, in which knowledge of the respondent’s HIV status by a friend, teacher/principal or last sexual partner was coded as “1” and no knowledge of the respondent’s HIV status by a friend, teacher/principal or last sexual partner was coded as “0”.

#### PHYSICAL HEALTH AND MISSED SCHOOL.

Physical health was assessed with a single item on self-reported health over the past month: *How has your overall health been in the last month (30 days)? (poor, ok, good, very good)*.

Missed school due to illness was assessed with a single item: *In the last month, have you missed any days of school because you were too sick to attend? (yes, no, I don’t attend school)*.

#### STIGMA.

Two items from the enacted subscale of the Adolescents Living with HIV Stigma Scale (ALHIV-SS) (Pantelic, Boyes, Cluver, & Thabeng, 2018) were adapted for this survey.

The language was simplified, and a six-month time frame was specified: *In the last six months, has anyone treated you badly because of your HIV? Y/N; In the last six months, have you lost friends because of your HIV? Y/N*. Responses to these questions were combined into one binary measure of ‘any’ enacted stigma, in which a “yes” to either of the questions was coded as “1” and a “no” to both questions was coded as “0”.

## STATISTICAL ANALYSIS

Descriptive statistics included frequencies, means and standard deviations (SD) of all variables. Mixed effects logistic regression examined the independent associations between each variable and an experience of HIV-related mistreatment. Mixed effects multiple logistic regression was used to identify the odds of HIV-related mistreatment given the increased risk for inadvertent disclosure (i.e., missed school due to illness, poor health) and disclosure to non-family (any friend, teacher/principal or sexual partner's awareness of respondent's HIV status) while controlling for potential confounding variables (age, sex, food insecurity, housing quality). The adolescents sampled were from 126 peer support groups. Thus, a two-level random intercepts model was fit using the "melogit" command in STATA v17 with support group specified as the random effect. By default, the integration method is "mvaghermite", which performs mean-variance adaptive Gauss-Hermite quadrature. Ten integration points were specified to provide a more accurate approximation to the log-likelihood. Comparative model fit indices (Akaike's Information Criterion [AIC] and Bayesian Information Criterion [BIC]) were used to select the best-fitting model. All statistical inference used the 5% significance level. Data were analyzed using STATA v17 (Stata Corporation, College Station, Texas, USA).

## RESULTS

### SURVEY RESPONSE RATES

A total of 126 out of 128 groups participated within the 38 study sites. Among the 1,753 beneficiaries present on the survey day, 1,451 participants completed surveys.

Subsequently, 64 survey records were excluded due to conflicting age eligibility between program and survey records, and 114 were excluded because the youth denied their HIV status was positive (e.g., wrote "HIV-negative" on the survey or did not answer any of the 11 questions related to HIV status). Thus, the final baseline sample included 1,273 respondents. However, the final analysis population was limited to those with no item non-response on age [0], sex [0], housing [0], food insecurity [13]), health [12], school attendance [12], disclosure [44] and stigma [35] variables, for a total of 1,186 records. An ad hoc analysis was conducted to investigate whether respondents missing data on disclosure may vary in the outcome response while controlling for age and sex; however, there was no statistically significant difference between those with observed disclosure data and those missing disclosure data on an experience of enacted stigma. Thus, the expected magnitude of bias introduced by a listwise deletion approach is expected to be minimal.

### DESCRIPTIVE STATISTICS.

The average age of the analytic population was 16.8 years, and 63% were female (Table 1). Twenty-six percent reported recent food insecurity. Most participants reported that

their household had electricity (95%), indoor plumbing (56%) and non-dirt floors (79%). Forty-two percent reported poor or ok health, while 30% reported they missed school due to illness in the past month. Another 9% reported they were not currently in school. Ninety-six percent of respondents reported that a parent/caregiver, household member, teacher, friend or recent sexual partner was aware of their HIV status. On average, respondents reported that people representing at least two of the five prompted relationship types were aware of the respondent's HIV status. Eighty-nine percent (89%) of respondents stated that a parent or caregiver was aware of the respondent's HIV status. Additionally, two-thirds (66%) of respondents reported that everyone in their household knew their status. Fewer respondents reported that a friend (33%) or teacher (28%) knew their status. Of those sexually active (n=477), 49% reported that their most recent sexual partner was aware of their HIV status. This represented 20% of the sample as a whole. Over one-fifth (23%) of respondents reported an experience of HIV-related mistreatment in the last six months: Eighteen percent of respondents reported they were treated badly because of HIV, while 13% reported they had lost a friend because of their HIV status.

**Table 1:** Sample characteristics for analytic population (N=1186)

<b>Variable</b>	<b>n</b>	<b>%</b>	<b>Mean (SD)</b>
<b><i>Sociodemographic variables</i></b>			
Age in years (Mean, SD)			16.8 (1.9)
Female	752	63.4	
Recent food insecurity	307	25.9	
Electricity	1124	94.8	
Indoor Plumbing	666	56.2	
Non-dirt floors	938	79.1	
<b><i>Health and disclosure variables</i></b>			
Poor or ok health	502	42.3	
Did not miss school due to illness last month	716	60.4	
Missed school due to illness last month	<b>368</b>	30.0	
Not in school	102	8.6	
Non-family knows	647	54.6	
Parent/CG knows	1049	89.4	
Everyone in household knows	771	66.2	
Any friend knows	389	33.1	
Any teacher knows	323	27.5	
Most recent sexual partner knows (N=477)	233	48.9	
<b><i>Enacted stigma variables</i></b>			
Treated badly due to HIV status	220	18.6	
Lost a friend due to HIV status	153	12.9	
Any HIV-related mistreatment	276	23.3	

## MIXED EFFECTS LOGISTIC REGRESSION

**Table 2** shows crude and adjusted odds ratios of reporting an experience of HIV-related mistreatment in the past six months. In crude analyses, age and gender were not significantly associated with HIV-related mistreatment. Experiencing food insecurity was associated with more than double the odds of reporting HIV-related mistreatment (OR=2.46, 95% CI=1.80-3.35). Living in a household with electricity was associated with significantly reduced odds (OR=0.35, 95% CI=0.20-0.64), while indoor plumbing and non-dirt floors were not associated with HIV mistreatment. These latter two housing indicators were subsequently dropped from the adjusted analyses.

Factors that may inadvertently disclose one's HIV status were also associated with HIV-related mistreatment. Respondents who reported poor or ok health had much higher odds of experiencing mistreatment than those who reported good or very good health (OR=2.02, 95% CI=1.51-2.71). In addition, respondents who missed school due to illness in the past month had increased odds of mistreatment compared to those who did not miss school (OR=2.20, 95% CI=1.61-3.00).

Non-family knowing the respondent's HIV status was associated with more than two-fold higher odds of HIV-related mistreatment (OR=2.49, 95% CI=1.83-3.38). When knowledge of the respondent's HIV status was examined by individual relationship types, any friend (OR=2.29, 95% CI=1.70-3.08), any teacher or principal (OR=1.89, 95% CI=1.38-2.58), and most recent sexual partner (OR=1.97, 95% CI=1.40-2.77) were each associated with a recent experience of HIV-related mistreatment. Parent or caregiver

knowledge of the respondent's HIV status and household members' knowledge was not associated with HIV-related mistreatment.

In the adjusted analyses, poor or ok health (OR=1.53, 95% CI=1.13-2.09), missed school due to illness (OR=1.67, 95% CI=1.21-2.32), and non-family knows HIV status (OR=2.12, 95% CI=1.54-2.92) remained associated with HIV-related mistreatment. Experiencing recent food insecurity was associated with higher odds of HIV-related mistreatment (OR=1.80, 95% CI=1.30-2.50), while having a home with electricity (OR=0.48, 95% CI=0.26-0.87) was associated with lower odds of HIV-related mistreatment.

**Table 2.** Unadjusted and adjusted baseline odds ratios for factors associated with an experience of HIV-related discrimination in the past six months (n=1,186)

	Logistic Regression				Multiple logistic regression					
	Crude OR	(95% CI)		P-value	Adjusted OR	(95% CI)		P-value		
		LI	UI			LI	UI			
<b>Fixed Effects</b>										
<i>Sociodemographic variables</i>										
Age in years	1.03	0.95	1.12	0.485		1.00	0.91	1.09	0.915	
Female	1.02	0.75	1.38	0.922		0.98	0.71	1.35	0.899	
Recent food insecurity	2.46	1.80	3.35	0.000	***	1.80	1.30	2.50	0.000	***
Electricity	0.35	0.20	0.64	0.001	**	0.48	0.26	0.87	0.016	*
Indoor Plumbing	0.97	0.72	1.30	0.817						
Non-dirt floors	1.36	0.96	1.93	0.080						
<i>Health and school attendance</i>										
Poor or ok health	2.02	1.51	2.71	0.000	***	1.53	1.13	2.09	0.007	**
Did not miss school due to illness last month	REF	REF	REF	REF		REF	REF	REF	REF	
Missed school due to illness	2.20	1.61	3.00	0.000	***	1.67	1.21	2.32	0.002	**
Not in school	1.54	0.91	2.61	0.105		1.24	0.71	2.17	0.444	
<i>Disclosure</i>										
Non-family knows	2.49	1.83	3.38	0.000	***	2.12	1.54	2.92	0.000	***
Parent/CG knows	0.94	0.58	1.52	0.790						
Everyone at home knows	1.11	0.73	1.37	0.995						
Any friend knows	2.29	1.70	3.08	0.000	***					
Any teacher knows	1.89	1.38	2.58	0.000	***					
Most recent sexual partner knows	1.97	1.40	2.77	0.000	***					
<b>Random Effect</b>										
Peer support group						0.42	0.20	0.88		

OR, Odds Ratio; CI, confidence interval; CG, caregiver;

\*\*\*p&lt;0.001, \*\*P&lt;0.01, \*P&lt;0.05



## DISCUSSION

This study found that almost a quarter of adolescents and young adults living with HIV and enrolled in structured support groups in urban communities in South Africa experienced recent enacted stigma. Results are comparable to the handful of other studies that have measured experiences of HIV-related enacted stigma among young people in Southern Africa (Mugo et al., 2021; Pantelic et al., 2020) and other low and middle-income countries (LMIC) (Aurpibul et al., 2020). Results are also similar to the one in four adults reporting experiences of stigma in the last 12 months across multiple communities in South Africa (Stangl et al., 2020).

Over ninety percent of adolescents reported that someone else knew their HIV status. Caregivers were the most frequently reported relationship type to be aware of the respondent's status, which may reflect the importance of family in pediatric disease management and the presence of perinatally acquired HIV in the sample. Previous research from South Africa has highlighted that caregivers' knowledge of adolescent serostatus is important for facilitating care (Denison et al., 2015; Maskew et al., 2016). Beyond the family, more than half the sample reported that a friend, teacher, principal or their most recent sexual partner was aware of their status. These findings are comparable to a smaller study among youth living with HIV in Kenya, which measured who knew adolescents and young adult's HIV status (defined as *any disclosure*) and to whom adolescents had directly told their status (defined as *self-disclosure*) (Mugo et al., 2021). When *any disclosure* was measured, 91% of the Kenyan sample reported someone else

knew their status, of which over two-thirds reported family member/s knew and around one-third reported that non-family member/s knew.

Knowledge of one's HIV status outside of the family or household was associated with double the odds of enacted stigma, even after controlling for factors that may be associated with inadvertent disclosure. In contrast, the study among youth in Kenya found a larger association between experienced and internalized stigma and self-disclosure to family than disclosure to non-family (Mugo et al., 2021). However, the Kenyan sample had a high prevalence of behaviorally acquired HIV and older adolescents and young adults were more likely to have self-disclosed to family than younger adolescents. Thus, the Kenyan findings may reflect unique dynamics between perinatally and behaviorally acquired HIV, as the latter mode of transmission increases with age. Adolescents with behaviorally acquired HIV may experience significant challenges disclosing their status to parents or caregivers (Thoth, Tucker, Leahy, & Stewart, 2014).

Each non-family relationship type – friend, teacher/principal, and most recent sexual partner – was associated with HIV-related mistreatment in unadjusted analyses. These findings support qualitative research from East and South Africa that highlight concerns around status disclosure among peer networks and within school environments (Loveday et al., 2022; S. Madiba & Mokgatle, 2016; Onyango et al., 2021). For example, adolescents in KwaZulu-Natal describe concerns about disclosing their status to friends, fearing they would be gossiped about and rejected (Loveday et al., 2022). Kenyan

students described teachers' violating confidentiality and experiences of bullying, ridiculing and isolation by school staff and students alike (Onyango et al., 2021).

In this study, only half of the sexually active sample reported that their most recent sexual partner was aware of their HIV status, and awareness was associated with HIV-related mistreatment. Other studies have shown that disclosure to romantic or sexual partners is among the most challenging types of disclosure and is affected by the HIV status of the partner and the kind of relationship (e.g., casual vs. main) (Thoth et al., 2014). Among sexually active people in South Africa, disclosure to sexual partners is low, with rates of 23% in a nationally representative sample of people living with HIV age 15 and older (Simbayi et al., 2017). Rates of disclosure to sexual partners by youth reported elsewhere in South Africa (Kidman & Violari, 2020) are also low. As with broader peer networks, qualitative evidence suggests that a fear of rejection inhibits sharing one's HIV status (Loveday et al., 2022).

These results support calls for careful attention to the full consequences of disclosure among young people (Kidman & Violari, 2020; Thoth et al., 2014). While recognizing the limited evidence base around adolescent disclosure, the World Health Organisation recommends that adolescents be counseled and empowered to decide when, how and to whom to disclose their HIV status (WHO, 2013). Individualized disclosure counseling by healthcare or social workers may support young people in assessing and managing the different degrees of risk and benefit involved with disclosure, especially as their social networks expand and change with age. Indeed, youth living with HIV have emphasized

the importance of making their own choices around disclosure and requested support to develop skills for decision-making, initiating discussions, and managing adverse reactions (Thoth et al., 2014; WHO, 2013). However, providers may experience challenges adequately addressing disclosure with adolescents during limited engagements (WHO, 2013).

Similar to another study examining HIV-related disability (Pantelic et al., 2017), this study found that factors that may inadvertently disclose one's HIV status, including missing school due to illness and poor self-rated health, were associated with increased odds of a recent experience of HIV related mistreatment. The physical manifestation of disease often drives the fear that results in stigma; thus, mistreatment may lessen as health is restored. At a community level, widespread initiation and adherence to ART are expected to reduce enacted stigma via the power of healthy appearances (Camlin et al., 2020). At an individual level, supporting adolescents to adhere to ART, and manage side effects and opportunistic infections, may ease anxieties around unintentional disclosure. Further, holding clinic appointments outside of school hours may help reduce school absences and improve retention in care (Zanoni, Sibaya, Cairns, & Haberer, 2019). However, while it is possible that community members associated poor health or missed school with HIV-related illness, it is also possible that the reported mistreatment occurred *within* healthcare settings. Research from South Africa and elsewhere has highlighted the detrimental effects of healthcare discrimination on the continuum of care outcomes among adolescents and adults living with HIV (Algarin et al., 2020; Pantelic et al., 2020; Turan, Rogers, et al., 2017).

These findings suggest that broader community stigma reduction is needed. However, while stigma has a well-documented negative impact on the health and well-being of people living with HIV (Katz et al., 2013; Rao, Kekwaletswe, Hosek, Martinez, & Rodriguez, 2007; Sweeney & Vanable, 2016), rigorous evidence is lacking for HIV stigma-reduction interventions (Andersson 2020; Stangl 2013; Smith 2020), particularly among adolescents (Gavan et al., 2022; Hartog et al., 2020). Limited evidence suggests the effects of HIV-related mistreatment may be ameliorated by strengthening secure social support networks through clinic-based peer support groups (Mavhu et al., 2020; Woollett, Pahad, & Black, 2021; Zanoni et al., 2019) and family-centered programming (Bhana et al., 2014).

This study reached a large community-based sample of adolescents living with HIV in a high HIV prevalence setting. Adolescents were recruited to participate in the survey from peer support groups provided by community-based organizations and may differ systematically from youth who choose not to or are unable to participate in structured interventions offered by community-based organizations. Due to the brevity of the research tool, this study did not use the complete ALHIV-SS instrument or assess whether the adolescent had intentionally self-disclosed their HIV status, the extent to which disclosure occurred, or whether additional relationship types (e.g., neighbors, church members, work colleagues, or community leaders) were aware of their status. Temporality and causality cannot be established with the cross-sectional survey design. In particular, the time frame for the survey questions on HIV-related mistreatment was six months, while that for health and school absences was only the past month. Even if the time frames were similar, reverse causality could not be ruled out, as an experience of HIV-related

mistreatment may have resulted in poor self-rated health and school absences. For example, people who experience HIV stigma are at higher risk for reduced care-seeking behaviors (Dlamini et al., 2009; Kalichman & Simbayi, 2003; Naar-King et al., 2007) and poorer physical health (Rueda et al., 2016). Future research should use longitudinal mediation studies to establish the temporal relationship and causal pathway between physical health and enacted stigma. In the meantime, this study contributes to the limited knowledge of HIV-related stigma and its correlates among adolescents and young adults.

## PAPER 2. PATHWAYS FROM HIV-RELATED ENACTED STIGMA TO SUB-OPTIMAL ART ADHERENCE AMONG YOUNG PEOPLE LIVING WITH HIV IN SOUTH AFRICA

### INTRODUCTION

Globally, 1,710,00 million adolescents (aged 10-19) were living with HIV in 2021, including approximately 320,000 in South Africa (UNICEF, 2022b). Despite a marked increase in the number of adolescents initiating HIV treatment in South Africa's public sector program (Maskew et al., 2019), adolescent viral suppression rates remain low (Zanoni et al., 2016). Studies from South Africa indicate that adolescents and young adults have lower retention in care and ART adherence than other age groups in South Africa (Evans et al., 2013; Nachega et al., 2009).

Globally, HIV-related stigma is a well-documented risk factor for suboptimal ART adherence though the evidence base is mainly among adults (Katz et al., 2013; Rueda et al., 2016; Sweeney & Vanable, 2016). Among young people living with HIV in South Africa, HIV-related stigma has been linked to reduced retention in HIV care (Pantelic et al., 2020) and lower ART adherence (Loveday et al., 2022). Stigma is the social devaluation of a person based on an attribute associated with negative public attitudes (Goffman, 1963). Potential explanations for stigma as a barrier to adherence include fear of inadvertent disclosure, loss of social support, and increased vulnerability to poor mental health (Katz et al., 2013; Logie et al., 2018; Sweeney & Vanable, 2016).

However, more rigorous research is needed on the mechanisms through which different dimensions of stigma compromise HIV-related health outcomes (Katz et al., 2013; Sweeney & Vanable, 2016). Furthermore, compared to adults, very few studies have explored mediators and moderators of stigma on ART adherence among youth (Martinez et al., 2012; Pantelic et al., 2020).

Multiple dimensions of HIV-related stigma at the individual level have been defined and are presumed to impact people living with HIV differently (Earnshaw & Chaudoir, 2009). For example, *enacted stigma* is the direct experience of devaluation or discrimination because of one's HIV status, while *internalized stigma* is the self-endorsement of negative attitudes about HIV, resulting in feelings of shame, guilt, and worthlessness. ART adherence behaviors are theorized to have a stronger relationship with *internalized* HIV-related stigma than other dimensions of HIV-related stigma (Turan et al., 2019). Different dimensions of stigma may also influence each other, and the relationship between enacted and internalized stigma is particularly important (Fazeli et al., 2017; Turan, Hatcher, et al., 2017). Adolescents may be especially susceptible to internalizing stigma after experiencing HIV-related discrimination due to the weight assigned to peer approval and inadequately developed coping skills (Patel, Flisher, Hetrick, & McGorry, 2007). However, few studies among adolescents living with HIV in sub-Saharan Africa have investigated the prevalence or drivers of internalized stigma (Pantelic, Shenderovich, Cluver, & Boyes, 2015) or pathways between different dimensions of stigma (Pantelic et al., 2017; Pantelic et al., 2020).



Adolescents living with HIV in South Africa experience high rates of psychological distress, including depression, anxiety, and post-traumatic stress disorder (Boyes, Cluver, Meinck, Casale, & Newnham, 2019; Sherr, Cluver, Toska, & He, 2018; Woollett, Cluver, Bandeira, & Brahmhatt, 2017). Mental health, including psychological distress, is another potential mediating mechanism from stigma to adherence (Turan, Hatcher, et al., 2017). Several longitudinal analyses have provided robust support for the mediating role of depression on internalized stigma and treatment adherence outcomes among North American adults (Christopoulos et al., 2020; Turan et al., 2019). In contrast, anxiety has rarely been investigated with rigorous quantitative studies (Rueda et al., 2016). Understanding the role of psychological distress in adherence pathways may be especially salient for adolescents, given the increased emergence of mental health disorders during this developmental stage (Patel et al., 2007). Further, internalized stigma has been identified as a correlate of psychological distress in this population (Boyes et al., 2019).

This study aims to test a conceptual model of associations and pathways between HIV-related discrimination and past-month ART adherence via HIV-related shame and psychological distress (depression, anxiety) among youth living with HIV in South Africa. The conceptual model for this study (see Figure 1) builds on the aforementioned literature and Turan et al.'s (2017) conceptual framework. Turan et al.'s framework focuses on the differential effects of individual-level dimensions of stigma, including enacted and internalized, and potential individual and interpersonal mechanisms explaining how stigma affects HIV-related health at an individual level.

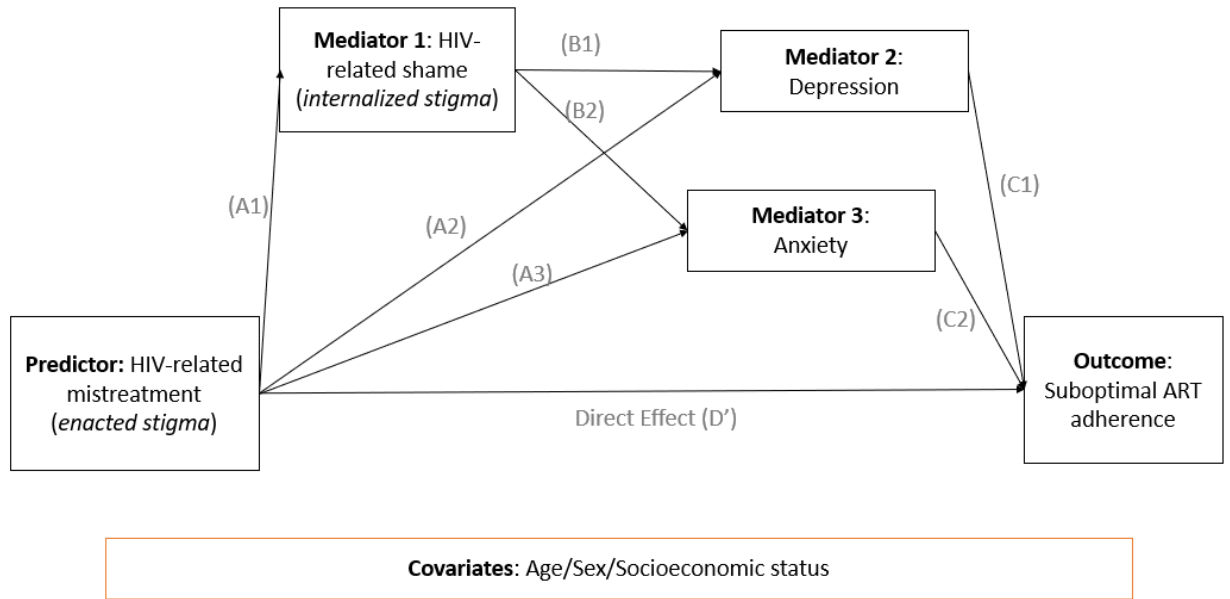


Figure 1. Hypothesized risk pathway from HIV-related mistreatment to sub-optimal ART adherence.

## METHODS

The study design is a cross-sectional analysis of baseline survey data from an evaluation designed to understand potential program effects on ART initiation and adherence among adolescents living with HIV. In brief, surveys were conducted among youth newly enrolled in a structured support group intervention (Vhutshilo 3) between June 2019 and March 2020 at urban program sites in KwaZulu-Natal and Gauteng provinces. Study eligibility was predicated on program eligibility (ages 14-24, awareness of their HIV-positive status, and English speaking) and willingness to participate in the survey. Subjects who did not wish to participate in the survey were still encouraged to join in the Vhutshilo 3 intervention. The one-hour survey was administered in English by external researchers to each Vhutshilo 3 group, whereby the researcher read each question aloud to the group, and participants self-reported their answers on a paper form. Confidentiality was maintained

by using coded identifiers, ensuring sufficient spacing between seats, and asking participants to seal their completed questionnaire in an individual envelope before returning it to the research staff. Upon completing the survey, participants received refreshments and a small monetary reimbursement for their time (ZAR 20, approximately US\$1.20).

### ETHICAL CONSIDERATIONS

The study was reviewed and approved by The Social Behavioral Institutional Review Board at Tulane University in the U.S. (study reference no: 2018-1736) and Pharma Ethics Independent Research Ethics Committee in South Africa (study reference no: 181021579). Written voluntary informed consent for survey participation was sought for all participants before survey administration. The Tulane and Pharma Ethics review boards waived parental permission for adolescents under 18.

### SURVEY MEASURES

**SOCIODEMOGRAPHIC CHARACTERISTICS.** Age, gender and socioeconomic status were included as control variables. Socioeconomic status was measured via questions on food insecurity and housing quality. Lower housing quality was defined as reporting less than two of three basic amenities: indoor plumbing, non-dirt-flooring, and electricity. Food security was assessed with one item of the Household Hunger Scale (Ballard et al., 2011) that focused on missing a meal due to a lack of food in the household in the past week.

**STIGMA.** Two items related to enacted HIV-related stigma (treated badly, lost friends) and one item related to internalized HIV-related stigma (ashamed of HIV status) were adapted from the Adolescents Living with HIV Stigma Scale (ALHIV-SS) (Pantelic et al., 2018). Responses to the questions on enacted stigma were combined into one binary measure of ‘any’ enacted stigma, in which a “yes” to either of the questions was coded as “1” and a “no” to both questions was coded as “0”.

**PSYCHOLOGICAL DISTRESS.** The ten-item Child Depression Inventory – Short Form (Kovacs, 2015) measured depressive symptomology (Cronbach’s  $\alpha = .75$ ). The respondent is asked to select the phrase that best represents how they felt in the last two weeks (e.g., “I feel like crying every day”/“I feel like crying most days”/“I feel like crying once in a while”). Each item is scored as “0” for no symptom, “1” for mild and “2” for definite symptoms. Scores range from 0-20, and higher CDI scores indicate more depressive symptomology. A six-item subscale of the Revised Children’s Manifest Anxiety Scale (Reynolds & Richmond, 1978) was used to measure worry (Cronbach’s  $\alpha = .67$ ). Responses were dichotomized as yes (1) or no (0) and summed for a range of 0-8.

**PAST-MONTH ART ADHERENCE.** The adherence outcome is based on a single item from Wilson’s adherence scale that measures the number of days with missed ART doses in the preceding 30 days (Wilson et al., 2014). The variable was dichotomized using a cut-off of greater than or equal to 90% past month adherence, meaning three or fewer days were missed in the past 30 days.

## STATISTICAL ANALYSIS

### DESCRIPTIVE AND REGRESSION ANALYSES

Descriptive statistics of all variables included frequencies, means and standard deviations (S.D.). A mixed effects model was tested to account for potential similarities of adolescents within support groups; however, the between-groups variance estimate was zero, so the random effect for the group was unnecessary. Unadjusted and adjusted logistic regression models were used to identify the odds of  $\geq 90\%$  past month ART adherence given the predictors of interest. All statistical inferences were set at the 5% significance level. Data were analyzed using STATA v17 (Stata Corporation, College Station, Texas, USA).

### STRUCTURAL EQUATION “PATH” MODELING

Structural equation modeling (SEM) refers to a family of related procedures that offer a theory-driven analytical approach for causal inference (Muellar & Hancock, 2019). The emphasis is on evaluating *a priori* specified hypotheses about causal relations among latent or measured variables. Measured variables path analyses (“path analysis”) is a type of SEM in which all variables are observable (Kline, 2016). Path analysis was used to identify significant pathways between HIV-related discrimination and past-month ART adherence via HIV-related shame and psychological distress (depression, anxiety). Given the binary nature of the outcome ( $\geq 90\%$  adherence), a generalized structural equation model (GSEM) was used. Each mediating variable’s family and link function were also specified to ensure estimation methods were adjusted accordingly. Results are presented as unstandardized regression coefficients ( $\beta$ ) for all paths adjusted for covariates.

## RESULTS

### DESCRIPTIVE STATISTICS

The baseline sample includes 1,273 participants who met all study inclusion/exclusion criteria. For this analysis, the dataset was then limited to respondents that reported they were currently on ART (n=857) with complete data on the predictors and outcome, resulting in an analytic dataset of 760 individuals. Among predictors, depression was the only predictor missing more than ten observations (n=34 observations missing; 4%). The participant's sex and age differed between those with and without complete depression data. A one-unit increase in age was associated with increased odds for observed data on depression, while females had higher odds for observed data on depression than males. Among the 55 respondents excluded for missing data on the outcome, participants' sex, age and socioeconomic status did not significantly differ between those with and without complete data on ART adherence. However, a one-unit increase in the depression score was associated with lower odds of having observed data on the ART adherence outcome (AOR = .90; p=0.017) in this survey. In other words, younger adolescents and males were more likely to be missing data on depression, and depressed individuals were more likely to be missing data on ART adherence. To estimate the magnitude of selection bias this may introduce, an additional analysis compared ART adherence between those with observed depression data and those missing depression data while controlling for age, sex and food insecurity. There was no significant difference between the two groups on the outcome of interest, so listwise deletion was used.

**Table 1** provides the characteristics of the final analytic sample. The average age of the sample was 17 years, and 69% were female. Twenty-seven percent reported recent food insecurity and 36% reported lower housing quality. Forty-two percent of respondents reported a CDI-10 score of 3.5 and an RCMAS worry sub-scale score of 4.0. Forty-four percent reported feeling ashamed of their HIV status (internalized stigma), and almost 24% reported an experience of enacted stigma in the past six months. Most of the sample, 81.2%, reported 90% or higher past month adherence.

#### LOGISTIC REGRESSION

**Table 2** shows the results of the crude and adjusted logistic regression models. In unadjusted analyses, food insecurity, CDI score, RCMAS worry sub-scale score, internalized stigma, and enacted stigma were each associated with the outcome. However, only food insecurity, the RCMAS worry sub-scale score and enacted stigma remained significant in the adjusted model. Reporting recent food insecurity resulted in lower odds of adherence (AOR=0.63, 95%CI=0.42-0.95), as did an increase in the anxiety score (AOR=0.83, 95%CI=0.72-0.95) and an experience of enacted stigma in the past six months (AOR=0.61, 95% CI=0.40-0.94).

**Table 1:** Sample characteristics for ALHIV currently on ART (n=760)

	N	%	Mean (SD)
<i><b>Sociodemographic variables</b></i>			
Age (mean, SD)			17.02 (1.90)
Female	525	69.1	
Food insecure	202	26.6	
Lower housing quality (<2 amenities)	272	35.8	
<i><b>Psychological Distress</b></i>			
CDI Score (mean, SD)			3.51 (3.44)
RCMAS Score (mean, SD)			4.00 (1.66)
<i><b>Stigma &amp; ART adherence variables</b></i>			
Internalized stigma (ashamed of HIV status)	336	44.2	
Enacted stigma in past six months (lost friend and/or treated badly because of HIV status)	180	23.7	
90% or greater adherence in the past 30 days	618	81.3	



**Table 2.** Unadjusted and adjusted odds ratios of  $\geq 90\%$  ART adherence in the past 30 days (n=760)

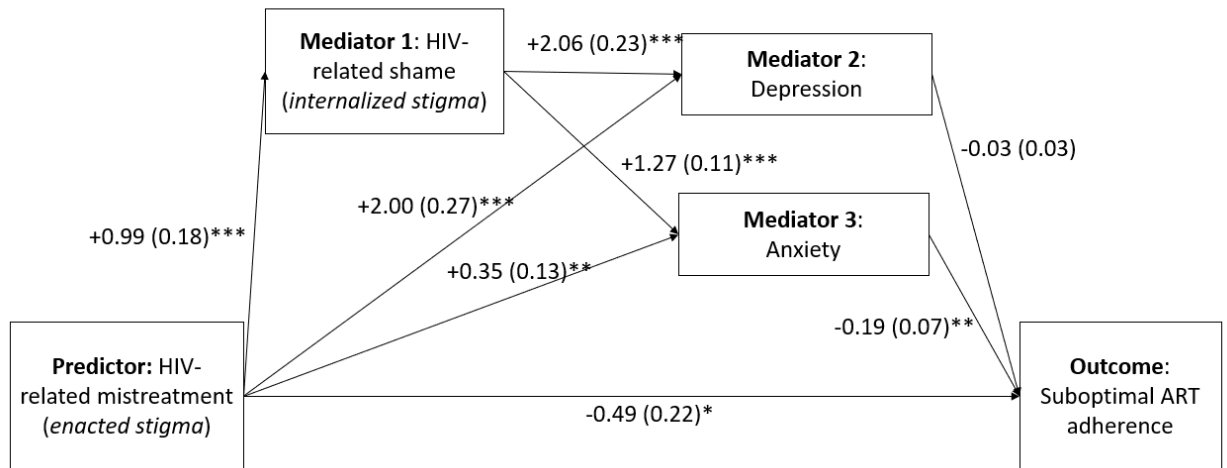
	Logistic Regression				Multiple Logistic Regression					
	Crude OR	(95% CI)		P-value	Adjusted OR	(95% CI)		P-value		
		LI	UI			LI	UI			
<i>Sociodemographic variables</i>										
Age	0.99	0.90	1.09	0.859		1.01	0.91	1.12	0.867	
Female	1.09	0.74	1.61	0.674		1.21	0.81	1.82	0.356	
Food insecurity	0.51	0.35	0.76	0.001	***	<b>0.63</b>	0.42	0.95	0.029	*
Lower housing quality (<2 amenities)	0.69	0.47	0.99	0.049	*	0.70	0.48	1.02	0.062	
<i>Psychological Distress</i>										
CDI Score	0.92	0.87	0.96	0.000	***	0.97	0.91	1.03	0.286	*
RCMAS Score	0.79	0.69	0.89	0.000	***	<b>0.83</b>	0.72	0.95	0.008	*
<i>Stigma variables</i>										
Internalized stigma (ashamed of HIV status)	0.63	0.44	0.91	0.014	**	0.99	0.65	1.51	0.961	
Enacted stigma in past six months (lost friend and/or treated badly because of HIV status)	0.47	0.32	0.70	0.000	***	<b>0.61</b>	0.40	0.94	0.025	*

OR, Odds Ratio; CI, confidence interval

\*\*\*p<0.001, \*\*P<0.01, \*P<0.05

## PATH ANALYSIS

The path analysis indicated that the effect of HIV-related mistreatment on 90% adherence is partially mediated by multiple pathways and an adjusted direct effect between mistreatment and adherence ( $\beta = -0.49$ , 95% CI = -0.92, -0.06). Four mediation pathways were investigated, of which only those including anxiety affected ART adherence. The first significant mediation pathway was between HIV-related mistreatment and anxiety ( $\beta = 0.35$ , 95% CI = -0.09-0.61). The second significant pathway was from HIV-related mistreatment to HIV-related shame ( $\beta = 0.99$ , 95% CI = 0.65-1.34) and from HIV-related shame to anxiety ( $\beta = 1.27$ , 95% CI = 1.04-1.49). Both pathways concluded with anxiety to ART adherence ( $\beta = -0.19$  (95% CI = -0.32—0.06)). In contrast, depressive symptomology was not a significant mediator between either dimension of stigma and ART adherence ( $\beta = 0.03$ , 95% CI = -0.09-0.02) in this model. Though, there was a direct effect of enacted stigma on depressive symptomology ( $\beta = 1.97$ , 95% CI = 1.44-2.50) and internalized stigma also partially mediated the relationship between HIV-related mistreatment and depressive symptomology ( $\beta = 2.06$ , 95% CI = 1.60-2.52). The covariance between depressive symptomology and anxiety was also significant (Coefficient = .86, 95% CI = .522-1.2). The final model had 19 degrees of freedom with an AIC of 8993.399 and a BIC of 8481.432. See Figure 2 for details of the path analysis.



**Figure 2.** Path results for HIV-related discrimination and shame on ART adherence. Unstandardized coefficients are reported with the standard errors in parentheses. Statistical significance is denoted by \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ . The model controlled for age, sex, food insecurity, and informal housing.

## DISCUSSION

This study found that experiences of HIV-related mistreatment were associated with lower ART adherence in a large sample of South African youth (age 14-24) who reported current ART use. This study also tested a conceptual model of hypothesized pathways from enacted stigma to suboptimal ART adherence. HIV-related shame and anxiety mediated the relationship between HIV-related mistreatment and ART adherence, while depressive symptomatology did not.

This study adds to the limited quantitative evidence base for the association between stigma and HIV treatment outcomes among youth (Pantelic et al., 2020). Other studies have investigated different pathways between stigma dimensions and ART adherence among youth with conflicting results. In contrast to our study, a cross-sectional structural equation

model among community-traced adolescents aged 10-19 in Eastern Cape, South Africa, found no direct association between enacted stigma and internalized stigma (Pantelic et al., 2017). However, a longitudinal analysis from the same study reported that internalized stigma mediated the relationship between three different facets of enacted stigma and retention in HIV care (Pantelic et al., 2020), suggesting an important relationship between enacted and internalized stigma. In terms of the pathway between enacted stigma and adherence, there was no direct association between discrimination due to the adolescent's HIV status (being tested or losing friends) and retention in care; however, healthcare discrimination and discrimination due to a family member's HIV status were directly associated with reduced retention in care (Pantelic et al., 2020). The difference in findings may be due to the younger sample in the Eastern Cape, as the majority were under 15 years of age, and their composite outcome, since retention in care combined self-reported past week adherence >85% with no missed clinic visits in the past year. For example, the involvement of caregivers likely plays a more significant role in attending clinic visits among younger adolescents than among older adolescents and young adults; thus, HIV-related discrimination that directly affects the caregiver may play a greater role in treatment retention than discrimination experienced by the child.

Depression is a risk factor for poor ART adherence and viral suppression among youth across income settings (Vreeman et al., 2017), including South Africa (Haas et al., 2023; Haas et al., 2020). However, in contrast to our hypothesis and prior mediation literature on HIV-related health outcomes in adults (Lo Hog Tian et al., 2021; Logie et al., 2018; Rao et al., 2012), depressive symptomology did not mediate ART adherence in this

sample. However, an experience of enacted stigma and internalized stigma were associated with depressive symptomology, which is consistent with prior research in adult populations from primarily high-income settings (Logie & Gadalla, 2009; Sweeney & Vanable, 2016; Turan et al., 2016) and among youth in Southeast Asia and South Africa (Aurpibul et al., 2020; Pantelic et al., 2017). In a study among adolescents and young adults with perinatally-acquired HIV in Thailand and Cambodia, a two-fold increase in depressive symptoms occurred among participants who experienced HIV-related discrimination (Aurpibul et al., 2020). This result was primarily driven by older participants, which the authors suggested may be due to a greater awareness of societal norms and judgments, increased emergence of mood disorders during mid-to-late adolescence, and increased onward disclosure of their HIV status (Aurpibul et al., 2020).

Reducing community stigma requires long-term structural changes (Grossman & Stangl, 2013; Stangl, Lloyd, Brady, Holland, & Baral, 2013). However, creating and tailoring interventions that target modifiable individual-level factors mediating HIV stigma and ART adherence may improve HIV treatment outcomes in the meantime. Almost half of the sample (44%) endorsed feeling ashamed of their HIV status, suggesting internalized stigma is common in this sample. However, the evidence base for internalized stigma reduction interventions for people living with HIV is small, and youth remain under-represented (Pantelic, Steinert, Park, Mellors, & Murau, 2019). Among individual-level approaches, psychological support and cognitive behavioral therapy have shown promising results among South African women (Peltzer et al., 2017; Tshabalala & Visser, 2011). However, interventions that include structural components combined with individual-level

approaches are more effective (Pantelic et al., 2019). Such multi-level interventions are likely necessary to address the differential effects of multiple dimensions of stigma experienced by people living with HIV (Logie et al., 2018; Turan, Hatcher, et al., 2017).

The survey reached a large sample of adolescents living with HIV, a hard-to-reach population at risk for poor health outcomes (Sohn & Bekker, 2021), using a simple survey tool administered under routine program operations. Limitations of this study included the self-administered survey modality, which increased the likelihood of missing data and the potential for misclassification of the ART adherence outcome. However, multiple studies have found correlations between self-reported ART adherence and viral suppression (Cluver et al., 2018; Usitalo et al., 2014). Further, a simple self-reported measure may be a valuable and efficient tool when more complex or expensive methods cannot be used (Wilson, Lee, Michaud, Fowler, & Rogers, 2016), as in this survey implemented during routine program operations. Nonetheless, the self-reported adherence outcome may overestimate adherence (Wilson et al., 2016). Further, longitudinal research suggests that adolescents report inconsistent adherence over time, implying that adherence reported at one point may mask high rates of temporal fluctuation (Zhou, Cluver, Shenderovich, & Toska, 2021).

The validity and reliability of psychometric survey instruments may also contribute to misclassifying exposure status. While research supports the underlying universality of the experience of depression and anxiety (Sweetland, Belkin, & Verdelli, 2014), there is a dearth of validated tools, particularly for use in child and adolescent mental health (Ali,

Ryan, & De Silva, 2016). To minimize the potential for bias, this study prioritized anxiety and depressive symptomology instruments with a previous history of use among adolescents living with HIV in South Africa (Boyes et al., 2019; Cluver et al., 2013; Woollett et al., 2017). For example, the psychometric properties of the RCMAS were previously assessed in a large South African community sample of children and adolescents, which confirmed the worry factor and reported a similar alpha (Boyes & Cluver, 2013).

Stigma researchers have also called for more robust measurement strategies (Turan, Hatcher, et al., 2017), and researchers in South Africa have adapted and validated a tool for measuring unique dimensions of stigma experienced by adolescents, the ALHIV-SS (Pantelic et al., 2018). However, the current study only utilized single-item measures of internalized and enacted stigma derived from the ALHIV-SS scale, limiting the ability to compare findings with other studies. The brief nature of the survey tool intentionally minimizes respondent burden, thereby limiting the length and nature of questions included. As a result, this study could not assess more nuanced and complex aspects of stigma, such as intersectional stigma due to multiple social statuses or identities (e.g., race, gender, class, sexual orientation).

Structural equation modeling allowed for a more nuanced understanding of pathways between different dimensions of stigma and ART adherence. However, an important limitation of structural equation modeling is the risk of confirmation bias (Kline, 2016), especially in cross-sectional analyses (Bryan, Schmiede, & Broaddus, 2007). Thus, it will

be critical to consider other explanations for the data, including equivalent or near-equivalent models. In addition, replicating this model across independent samples would be an essential next step (Kline, 2016). Finally, temporality and causality cannot be established with the cross-sectional survey design, and it may be difficult to delineate a clear mechanistic pathway. For example, while the present study looked at a pathway from internalized stigma to depression, an alternative pathway from internalized stigma to depressive symptoms is also possible (Pantelic et al., 2017). Therefore, future studies should employ longitudinal data analyses, including longitudinal sequential mediation analyses, to rule out reverse causation and better capture adherence dynamics over time.



# PAPER 3. LATENT CLASS ANALYSIS OF BARRIERS TO DAILY ART AMONG ADOLESCENTS AND YOUNG ADULTS LIVING WITH HIV IN SOUTH AFRICA

## INTRODUCTION

Globally, around one million adolescents (aged 10-19) living with HIV were receiving anti-retroviral therapy (ART) in 2021, an estimated 170,000 of whom lived in South Africa (UNICEF, 2022a). Adherence to ART is essential for HIV viral suppression and the associated reduction in morbidity and mortality, treatment resistance, and onward HIV transmission (Cohen et al., 2016; Eisinger, Dieffenbach, & Fauci, 2019; Harrigan et al., 2005; Paterson et al., 2000). However, adolescents living with HIV in South Africa and elsewhere in sub-Saharan Africa have lower adherence to treatment and viral suppression rates than other age groups (Adejumo et al., 2015; Evans et al., 2013; Nachege et al., 2009). Limited research also suggests that ART adherence and viral suppression are challenging for emerging adults (ages 20-24) (Kim et al., 2014; Simbayi et al., 2019).

HIV self-management requires adaptation and incorporation of ART into daily life (Eshun-Wilson et al., 2019), which may be additionally challenging for adolescents due to their unique developmental stage (Modi et al., 2012; Shaw, 2001). Reasons for nonadherence are complex and interrelated, yet they are often assessed in isolation. Understanding youth subgroups with co-occurring barriers to pill-taking and which patterns are most strongly associated with sub-optimal ART adherence may better inform intervention design and

population engagement. Latent class analysis (LCA) offers a person-centered analytic approach to make sense of a complex array of observed characteristics, behaviors, and symptoms (Collins & Lanza, 2010). Within the data, LCA identifies unobserved subgroups, denoted as classes, that exhibit similar patterns of characteristics or behaviors based on their endorsement of observed variables. This classification approach identifies internally homogenous (i.e., members of the subgroup endorsed similar patterns) and externally heterogeneous groups (i.e., differentiation across the groups is possible) (Collins & Lanza, 2010; Petersen et al., 2019). LCA is increasingly promoted as a statistical tool for developmental research because multiple aspects of individual functioning can be studied holistically (Lanza & Cooper, 2016).

As a well-established statistical approach, LCA has been used in various studies of medication self-management or ART adherence among adults in the U.S. and Europe (Blalock, Bosworth, Reeve, & Voils, 2019; Jaeger et al., 2012; Keiser et al., 2012; Meyers-Pantele et al., 2021; Voisin, Quinn, Kim, & Schneider, 2017). Among youth, LCA has been used to describe patterns of risk behavior or social and structural determinants associated with HIV acquisition among youth in sub-Saharan Africa (Comins et al., 2020; Mathur et al., 2020), and patterns of substance use and sexual risk behavior among young women living with HIV in the US (Clum, Chung, & Ellen, 2009). To our knowledge, LCA has not been used in studies among youth living with HIV in sub-Saharan Africa, possibly due to the large sample size recommended ( $n \geq 300$ ) (Weller, Bowen, & Faubert, 2020), which may be difficult to achieve among this relatively hard-to-reach population.

The primary objective of this study is to use latent class analysis to identify and characterize sub-groups of adolescents living with HIV who report current ART use based on similar patterns of modifiable individual-level reasons for missed ART doses. The secondary objectives are to understand whether subgroups covary on sociodemographic characteristics and whether subgroups predict ART adherence (i.e., taking 90% or more of ART doses in the past 30 days). We describe reasons for missed ART across all adolescents currently on ART to identify those patterns most likely associated with adherence below a 'good enough' threshold of 90%.

## METHODS

### STUDY DESIGN

The research design is a cross-sectional analysis of survey data acquired from the baseline round of an evaluation study of a structured peer support group for adolescents living with HIV. Participants aged 14-24 and aware of their HIV-positive status were recruited by community-based organizations serving orphans and vulnerable children and youth (OVY) in urban communities of Gauteng and KwaZulu-Natal, South Africa. The survey was self-administered on paper forms in the English language in a classroom setting. An external research team was present to manage the survey and ensure confidentiality. Written voluntary informed consent for survey participation was sought for all participants; a waiver of parental permission for adolescents under 18 was granted by Pharma Ethics Independent Research Ethics Committee in South Africa (study reference no: 181021579)

and The Social Behavioral Institutional Review Board at Tulane University in the US (study reference no: 2018-1736).

## SURVEY MEASURES

**REASONS FOR MISSED ART DOSES.** Respondents who self-reported that they were currently taking ART were asked: *Think about the last few times you missed taking your ARVs. What were the reasons?* Response options included *I forgot; I was feeling sick; I was worried the pills would make me feel sick; other people were around; and I did not think it would help.* These five reasons for missed ART were selected from a 24-item measure based on local consultation and prior literature highlighting common barriers among adolescents. The original measure was based on the Adult AIDS Clinical Trials Group Adherence Instruments (Chesney et al., 2000; Murphy, 2003) and the Adolescent Adherence Questionnaire (Naar-King & Templin, 2006; Pediatric AIDS Clinical Trials Group, 2004) and subsequently adapted for HIV-positive adolescents in South Africa, based on consultations with clinical experts and a Teen Advisory Group (Cluver, Toska, Wittesaele, et al., 2019). Items were dichotomized as endorsed (1) or not (0) in line with previous research (Blalock et al., 2019; Saberi et al., 2015).

**PAST-MONTH ART ADHERENCE.** Among respondents who reported currently taking ART (i.e., had taken any ART during the past 30 days), medication adherence was measured using a single item asking about the number of days with missed ART doses in the preceding 30 days (Wilson et al., 2014). A binary outcome was created with a cut-off for optimal adherence of 90% or higher in the past 30 days.

CONTEXTUAL VARIABLES. Sociodemographic variables included age, sex, food insecurity and housing quality. A single item measured food insecurity (*In the last month, have you ever gone a whole day and night without eating because there was not enough food in the house*). Lower housing quality was defined as reporting less than two basic amenities: indoor plumbing, non-dirt-flooring, and electricity. Two health access items focused on the clinic or hospital where the adolescent usually goes for medical care. One item measured travel time to the clinic (*On average, how long does it take you to get to the clinic or hospital where you usually go for medical care? Less than 30 minutes, 30 minutes to 1 hour, more than 1 hour*). A second item measured whether the respondent was treated well (*Overall, at the hospital or clinic where you usually go, how do the doctors and nurses treat you? Poor, OK [not good, but not bad], Good, Very Good*). Finally, two variables measured familial support for adherence in the form of a reminder to take ART on time (*Does someone at home usually remind you to take your ARVs when it is time to do so? Y/N*) and accompaniment by an adult to the clinic visits (*When you go to the clinic or hospital, does an adult you live with usually go with you? Y/N*). All variables were dichotomized except for age.

## ANALYSIS PLAN

### LATENT CLASS ANALYSIS

Latent class analysis was used to determine the unobserved group structure for daily ART barriers based on observed data for self-reported reasons for missed doses (See Figure 1). For each class solution, LCA produces two sets of parameters (Collins & Lanza, 2010).

The first parameter is the probability of membership in each latent class, and the second is the conditional probability that an individual in a particular class responds ‘yes’ to each indicator. These parameters are used to interpret and label the classes. Model assessment is an iterative process, starting with a two-class solution and proceeding until model identification cannot be achieved.

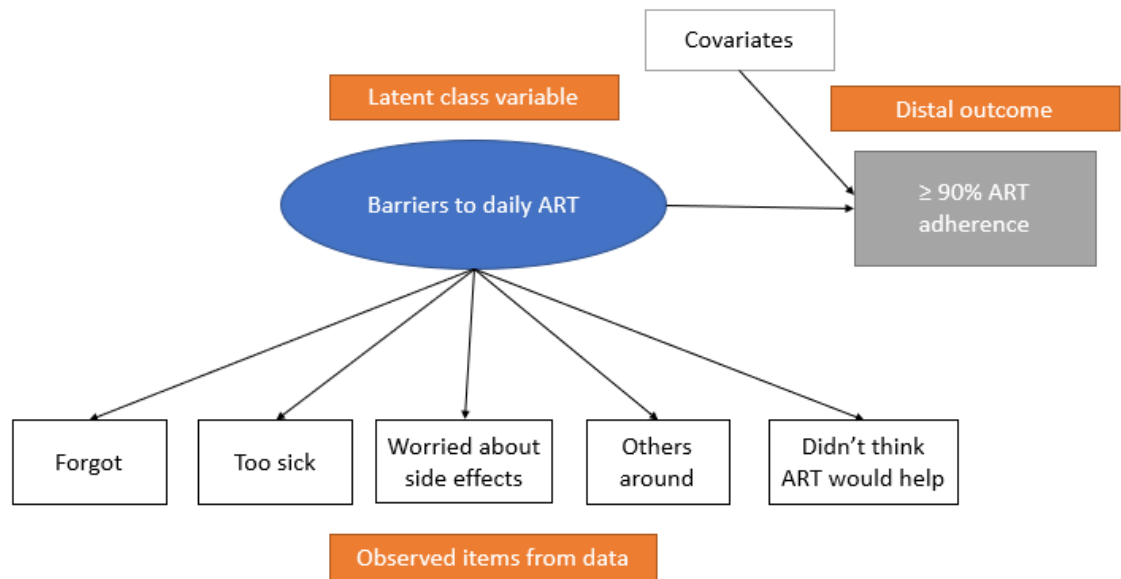


FIGURE 1. CONCEPTUAL MODEL FOR LATENT CLASS ANALYSIS OF BARRIERS TO DAILY PILL-TAKING WITH A DISTAL OUTCOME (≥90% ADHERENCE)

Comparative model fit indices (Akaike’s Information Criterion [AIC] and Bayesian information criterion [BIC]) were used to assess relative model fit, with lower Ics indicating a better-fitting model (Dziak, Coffman, Lanza, Li, & Jermin, 2020). The likelihood-ratio statistic ( $G^2$ ) was also used to assess how well the latent class model fits the observed data (Collins & Lanza, 2010). Finally, class separation and the findings’ theoretical and practical interpretability were also considered when selecting the optimal number of classes (Collins & Lanza, 2010). Good class separation minimizes uncertainty

regarding an individual's true class, which is necessary to apply the classify-analyze approach in subsequent analyses (Collins & Lanza, 2010). Data were analyzed using STATA v17 (Stata Corporation, College Station, Texas, USA) with maximum likelihood estimation.

#### MULTINOMIAL LOGISTIC REGRESSION ON SUBGROUP MEMBERSHIP

Youth were assigned a categorical variable representing their barriers to daily ART subgroup based on their highest posterior probability of class membership identified in the latent class analysis (Bray, Lanza, & Tan, 2015). This variable was used as the outcome for a multinomial logistic regression to determine whether the non-modifiable individual-level characteristics, age and sex, were associated with class membership.

#### LOGISTIC REGRESSION ON ART ADHERENCE

Finally, logistic regression measured the association of predicted membership in each subgroup on the outcome of  $\geq 90\%$  ART adherence while controlling for sociodemographic characteristics and contextual factors, such as health access and familial support.

## RESULTS

#### SAMPLE CHARACTERISTICS

The LCA sample included 857 baseline respondents who reported they were currently on ART (i.e., had taken ART in the past 30 days). **Table 1** provides the characteristics of the final analytic sample. Of the 857 respondents, the average age was 17, 67% were female, and half (47%) lived in Gauteng province. Twenty-seven percent reported recent food

insecurity, and 36% reported lower housing quality. Almost a quarter of respondents (24%) said it takes over an hour to get to their clinic or hospital, and 53% said an adult usually accompanied them. Most respondents (78%) said that someone at home reminds them to take their ARVs when it is time. Most respondents (82%) reported missing three or fewer doses in the past month for an ART adherence rate of 90% or higher. The most frequently endorsed reason for missing a dose was forgetting (35%), followed by other people around (27%), too sick to take ART (10%), worried pills would make them sick (8%), and did not think it would help (6%). Thirty-eight percent of respondents did not endorse any of the five reasons for missed doses, 44.6% endorsed a single reason, 13.0% endorsed two, and 4.4% endorsed three or more reasons.

**Table 1:** Sample characteristics and reasons for missed medication doses among youth living with HIV on ART (n=857)

<b>Variable</b>	<b>N</b>	<b>%</b>
<b><i>Sociodemographic variables</i></b>		
Gauteng	401	46.8
Age in years (Mean, SD)	17.0 (1.90)	
Female	577	67.3
Recent food insecurity	231	27.2
Lower housing quality (<2 amenities)	310	36.2
<b><i>Access &amp; support variables</i></b>		
Travel time to clinic >1 hour	204	23.8
Accompanied by adult	455	53.3
Someone at home reminds to take ART	667	78.2
<b><i>Reasons for missed doses</i></b>		
Forgot to take ART	302	35.2
Too sick to take ART	83	9.7
Worried pills would make sick	68	7.9
Other people around	229	26.7
Didn't think it would help	52	6.1
<b><i>Outcome</i></b>		
Past month ART adherence $\geq 90\%$	653	81.4

The following values were missing: food insecurity (n = 7), accompanied to clinic (n = 4), someone reminds to take ART (n=4), past month ART adherence (n=55)



## LATENT CLASSES OF PARTICIPANTS BASED ON REASONS FOR MISSED DOSES/S

**Table 2** provides fit criteria for the 1-class, 2-class and 3-class models. The 3-class model had the best fit on AIC (3445.681), while BIC was slightly higher than the 2-class model (3526.49). However, BIC often penalizes higher-class solutions (Collins & Lanza, 2010). The models with 1 and 2 latent classes had highly significant likelihood-ratio  $G^2$  test statistics ( $p < 0.0001$  for both tests), suggesting that a model with more than two classes was necessary to represent the population. The 3-class model had a  $G^2$  value of 18.87 with 17 df ( $p = 0.170$ ), suggesting that the observed data were not unlikely given the specified model. Further, the three-class solution had readily interpretable classes of reasonable size (i.e.,  $> 5\%$  each) with high maximum posterior probabilities for each class (i.e.,  $\geq 90\%$  each).

**Table 2.** Fit statistics and classification coefficients: Barriers to daily ART subgroups (classes)

Number of latent classes (K)	df	G2	p-value	AIC	BIC	LL
1	5	126.854	0.000	3529.667	3553.434	-1759.83
2	11	56.776	0.000	3471.589	<b>3523.877</b>	-1724.8
3	17	<b>18.868</b>	<b>0.170</b>	<b>3445.681</b>	3526.49	-1705.84
4	22	11.433	0.247	3448.246	3552.822	-1702.12

**Table 3** provides details of the basic class structure, including the marginal probabilities of endorsing each indicator based on given membership in a class. Class 1 was labeled as “Sick/Few Barriers” due to the likelihood of endorsing “too sick to take ART” (68%) and lack of endorsement on any other indicators. This class ( $n=53$ ) accounted for 9% of the sample. Class 2 ( $n=769$ ) was labeled as ‘Forgets/Few Barriers’ and accounted for 85% of the sample. Individuals classified within this group were more likely to endorse items “forgot” and “others were around” (37% and 27%, respectively) and had low levels of endorsement on all other items (5% or less). Finally, Class 3 ( $n=35$ ) had a 50/50 likelihood

of endorsing each of the indicators (47-62%) and was the least prevalent class (6%). This class was labeled as “Worries/Multiple Barriers” because the indicator with the highest likelihood of endorsement was “worried pills would make you sick” (62%), and individuals in this group often endorsed multiple barriers to adherence.

**Table 3.** Basic class structure: Latent class model representing barriers to daily ART subgroups (n=857)

Assigned label	Latent class		
	Sick n=53	Forgot n=769	Worries n=35
<i>Probability of membership</i>	0.09	0.85	0.06
<i>Conditional probability of endorsing indicator</i>			
Forgot to take ART	0.02	<b>0.37</b>	<b>0.56</b>
Too sick to take ART	<b>0.68</b>	0.01	<b>0.47</b>
Worried pills would make sick	0.01	0.05	<b>0.62</b>
Other people around	0.02	<b>0.27</b>	<b>0.52</b>
Didn't think it would help	0.04	0.03	<b>0.52</b>

#### ASSOCIATION OF DEMOGRAPHIC CHARACTERISTICS WITH SUBGROUP MEMBERSHIP

**Table 4** provides information on the associations from multinomial logistic regression between the predicted probability of belonging in one of the classes and age and sex. Class 2 (“Forgets/Few Barriers”) acted as the reference group because it had the largest size and minimal barriers to pill-taking. Class 1 (“Sick/Few Barriers”) did not differ from Class 2 based on age or sex. Females had a lower relative risk ratio for being in Class 3 (“Worries/Multiple Barriers”) relative to Class 2, though the results were not significant (RRR=0.56, 95% CI =0.29-1.12, p=0.10).

**Table 4.** Factors associated with barriers to daily ART subgroup class membership (n=857)

	Class 1				Class 3			
	RRR	(95% CI)		p-value	RRR	(95% CI)		p-value
		LI	UI			LI	UI	
<i>Sociodemographic variables</i>								
Age in years	0.88	0.75	1.03	0.13	1.01	0.85	1.21	0.88
Female	1.12	0.61	2.06	0.71	0.56	0.29	1.12	0.10

CI, confidence interval; RRR, relative risk ratio; Class 2 is the reference group

## ASSOCIATION OF SUBGROUP MEMBERSHIP WITH ART ADHERENCE

**Table 5** provides information on unadjusted and adjusted multiple logistic regression to identify the association of class membership with past-month ART adherence while controlling for sociodemographic, health access and familial support variables. Membership in Class 3 (“Worries/Multiple barriers”) was associated with lower adjusted odds (AOR=0.35, 95% CI=0.16-0.78) of reporting 90% or higher past month ART adherence relative to class 2 (“Forgets/Few barriers”). There was no association between age, sex, housing quality and adherence, but reporting food insecurity lowered the odds of adherence (AOR=0.61, 95% CI=0.41-0.91). Among health access and support variables, accompaniment by an adult to the clinic was associated with increased odds for adherence (AOR=1.66, 95% CI=1.13-2.47) as was reporting good or very good treatment by clinic staff (AOR=1.60, 95% CI=1.08-2.36). The pseudo R<sup>2</sup> for the final adjusted model was 0.0484.

**Table 5.** Unadjusted and adjusted baseline odds ratios for ART self-management class membership associations with  $\geq 90\%$  past month ART adherence (1=adherent, 0=non-adherent) (n= 788)

	Logistic Regression			P-value	Multiple Logistic Regression			P-value		
	Crude OR	(95% CI)			Adjusted OR	(95% CI)				
		LI	UI			LI	UI			
<b><i>Sociodemographic variables</i></b>										
Age in years	1.00	0.91	1.10	0.980		1.03	0.93	1.14	0.558	
Female	1.15	0.79	1.68	0.457		1.13	0.76	1.68	0.552	
Recent food insecurity	0.52	0.36	0.77	0.001	**	0.61	0.41	0.91	0.016	*
Lower housing quality (<2 amenities)	0.66	0.46	0.94	0.023	*	0.71	0.48	1.04	0.076	
<b><i>Access &amp; Support variables</i></b>										
Travel time to clinic >1 hour	0.63	0.42	0.93	0.021	*	0.71	0.47	1.08	0.106	
Treated well at the clinic	1.71	1.19	2.48	0.004	**	1.60	1.08	2.36	0.018	*
Accompanied by adult	1.56	1.09	2.23	0.016	*	1.66	1.13	2.47	0.011	*
Someone at home reminds to take ART	1.00	0.65	1.55	0.982		0.81	0.50	1.31	0.390	
<b><i>Class membership</i></b>										
Class 1 “Sick/Few Barriers”	0.75	0.37	1.51	0.427		0.74	0.35	1.57	0.435	
Class 2 “Forgets/Few Barriers”	1.98	1.18	3.35	0.010	*	REF	REF	REF	REF	
Class 3 “Worries/Multiple Barriers”	0.32	0.15	0.69	0.003	**	0.35	0.16	0.78	0.010	*

CI, confidence interval; OR, odds ratio

\*\*\*p&lt;0.001, \*\*P&lt;0.01, \*P&lt;0.05

## DISCUSSION

This study is the first known use of LCA to classify adolescents living with HIV based on self-reported reasons for missed doses. Additionally, it is the first to investigate the association of the emergent sub-groups with past-month ‘good enough’ ART adherence (Kahana, Rohan, Allison, Frazier, & Drotar, 2013). Rather than controlling individual-level variables to measure their independent effects, the goal was to understand the combined, synergistic effects of several relevant individual-level variables on ART adherence.

Three distinct classes emerged. Notably, the highest prevalence class (“Forgets/Few Barriers”) reported few barriers to pill-taking with only occasional endorsement of missing a dose due to forgetting or because others were around. The second most common class (“Sick/Few Barriers”) was characterized only by missing doses due to feeling sick. The survey did not elicit further details on the type or reasons for illness. However, the baseline sample reported a high prevalence of symptomology related to opportunistic infections, including tuberculosis (data not shown). Interestingly, the “sick” class did not endorse concerns about side effects or whether ART helps, which would be expected if there were concerns regarding the safety and efficacy of ART. The final class to emerge (“Worries/Multiple Barriers”) was characterized by its higher probability of endorsing each barrier, including forgetting, feeling sick, worrying about side effects or other people around, or because they did not think it would help. Worries about side effects and believing ART would not help were only endorsed within this group. This class had little homogeneity, implying a diversity of underlying response patterns. However, most response patterns included multiple barriers to adherence. A conceptually similar LCA on

self-reported reasons for missed doses to chronic medication among adult patients with hyperlipidemia identified a four-class solution despite including 21 possible reasons for missed doses (Blalock et al., 2019). Similar to our study, the largest class occasionally forgot, while a smaller class endorsed all or many reasons for missed doses (Blalock et al., 2019). However, the authors focused their latent class analysis on non-adherent adults, limiting the findings' ability to inform adherence screening tools.

This study described reasons for missed ART across all adolescents currently on ART to identify those patterns associated with adherence below a 90% threshold to identify individuals who could most benefit from targeted support. Eighty-one percent of adolescents reported missing three or fewer doses in the past month, and class membership predicted adherence. Adolescents who struggled with multiple barriers (class 3 "Worries/Multiple Barriers") were three times less likely to report 90% or higher past month ART adherence than adolescents who reported only occasionally forgetting or that others were around. While not statistically significant, adolescents who reported missing doses due to feeling sick (Class 1) were also slightly less likely to report optimal adherence than those who occasionally forgot or worried about others. These results align with a secondary analysis of longitudinal data on U.S.-based adults from 11 studies collected as part of the AIDS Clinical Trials Group (ACTG) (Saber et al., 2015), which examined longitudinal associations between self-reported adherence barriers and viral load among all participants on ART. Saber et al. (2015) found that most participants did not endorse any of the 14 listed adherence barriers and reported individual barriers at low frequency. However, the barriers with the greatest impact on virologic detectability were

often those least commonly endorsed, such as feeling sick, pill burden or concerns with safety or side effects. Forgetfulness, while one of the most common barriers, was not associated with reduced odds for virologic suppression. The study also found that individuals who reported more adherence barriers had lower odds of virologic suppression, suggesting a cumulative impact of barriers on adherence.

Findings suggest that forgetfulness, while common, is likely not the best indicator of poor HIV self-management or ART adherence capacity. As reported elsewhere (Saber et al., 2015), this may explain why controlled studies examining interventions focused on reminders, such as SMS messages, have limited or mixed findings regarding significant adherence improvements (Ridgeway et al., 2018). Findings also suggest that intervention engagement should focus on adolescents who report multiple barriers to adherence, especially those who report concerns about side effects or lack of belief in ART efficacy. Reviews suggest a strong association between patients' concerns and beliefs in medication efficacy and medication adherence (Horne et al., 2013; Langebeek et al., 2014). In South Africa, community-based approaches, including home visits from patient advocates, have demonstrated promise among children and adults to address the broad range of barriers affecting adherence (Fatti, Mothibi, Shaikh, & Grimwood, 2016; Fatti et al., 2014; Grimwood et al., 2012; Igumbor, Scheepers, Ebrahim, Jason, & Grimwood, 2011). However, it will be essential that patient advocates and other community health workers are trained in adolescent-friendly service provision, given that harsh or condescending treatment by adults can deter adolescents from care (Hanghøj & Boisen, 2014; Maskew et al., 2016).

Contextual factors such as food insecurity, being treated well at the clinic, and accompaniment to the clinic were also associated with 90% or higher past month ART adherence. This finding accords with research on ART adherence and clinic retention among adolescents in Eastern Cape, South Africa (Cluver et al., 2018), and may be amenable to targeted intervention via cash grants and social protection interventions, such as clinic transport subsidies (Cluver et al., 2016; Fahey, Njau, Dow, Kapologwe, & McCoy, 2019; Fahey et al., 2020; McCoy et al., 2017). However, the patient, friendly interactions with healthcare workers that improve adolescent retention in care may require structural adjustments to overburdened clinics in addition to healthcare worker training (Cluver et al., 2018). A longer travel time to the clinic was associated with lower odds of adherence in unadjusted but not adjusted analyses. Prior research suggests that older adolescents and young adults, in particular, may face more time pressure due to competing priorities between school, income generation, and household and family responsibilities (Maskew et al., 2016). In this sample, age and sex did not explain differences in class membership and were not associated with 90% adherence. Research from low and middle-income countries has found inconsistent results for the role of age and sex on adherence (Hudelson & Cluver, 2015). In contrast, previous research on other chronic conditions suggests that increasing age is often associated with a decline in self-management from childhood to adolescence (Modi et al., 2012).

While a threshold of 95% adherence is often cited as necessary for virologic suppression based on early research on combination anti-retroviral therapy with protease inhibitors (Paterson et al., 2000), practically, this means that only one daily dose could be missed in



30 days. However, multiple reviews suggest viral suppression may be achieved at lower levels of adherence based on improved ART treatment regimens (Bezabhe, Chalmers, Bereznicki, & Peterson, 2016; Byrd et al., 2019; Kahana et al., 2013). These include regimens containing integrase strand transfer inhibitors (INSTI), such as the first-line ART regimen for adolescents in South Africa under the 2019 treatment guidelines (NDoH, 2020). Further, since nonadherence is considered normative during this developmental stage, separating adolescents who occasionally miss a dose from those who miss many doses during a prolonged period may result in more meaningful intervention targeting.

Limitations of this study include the challenges of self-reported ART adherence outcome ascertainment and the potential for recall and social desirability bias. In addition, we were not able to capture all potential adherence barriers. For example, the type of ART regimen is a potential barrier among adolescents (Hudelson & Cluver, 2015; Natukunda, Cluver, Toska, Musiime, & Yakubovich, 2017). A limitation of the latent class analysis classify-analyze approach is the potential for misclassification of the exposure since individuals are assigned to a class based on predicted probabilities (i.e., the probability that they would be in a specific class). Further, two groups had small sample sizes (class 1 n=53 and class 3 n=35), which may reduce statistical power to detect differences. Finally, observational cross-sectional study designs are not designed to draw causal conclusions, and results should be interpreted cautiously. For example, adolescents with good adherence may be treated better at the clinics where they received care because they were considered compliant with medical authority. However, our goal was to explore possible associations between the classes identified and ART adherence to inform future research efforts rather

than establish causal associations. Future studies should measure medication adherence longitudinally, given that adherence is expected to vary over time (Zhou et al., 2021), potentially affecting class characteristics and membership from one point to the next.

This study is innovative in investigating individual-level barriers to youth adherence. By considering the influence of co-occurring barriers to adherence, this method identified subgroups of individuals at risk of poor ART adherence who may benefit from a focused intervention based on their common characteristics.

## DISCUSSION

This study used data from the PEPFAR OVCA&Y program in South Africa, among the largest programming efforts nationally to support vulnerable young people, to generate knowledge regarding modifiable individual-level and relational factors associated with HIV stigma and ART adherence.

The findings from the first two studies underscore the prevalence of stigma experienced by youth living with HIV. Close to a quarter of all adolescents in the sample reported an experience of HIV-related mistreatment in the past six months, while forty-four percent of those currently on ART reported feeling ashamed of their HIV status. In line with previous, primarily qualitative, research among youth in sub-Saharan Africa (Lambert et al., 2018; Loveday et al., 2022; Pantelic et al., 2017; Wolf et al., 2014), poor health and knowledge of HIV status outside the family were associated with HIV-related mistreatment. Experiences of HIV-related mistreatment were associated with lower ART adherence. In the conceptual model of hypothesized pathways from enacted stigma to suboptimal ART adherence, HIV-related shame and anxiety mediated the relationship between HIV-related mistreatment and ART adherence, while depressive symptomology did not. While this study adds to the limited quantitative evidence base for the association between stigma and HIV treatment outcomes among youth (Pantelic et al., 2020), findings are mixed compared to the few studies investigating pathways between stigma dimensions and ART adherence among youth (Pantelic et al., 2017; Pantelic et al., 2020) and the mediation literature on depression (Lo Hog Tian et al., 2021; Logie et al., 2018; Rao et al., 2012).

The third study investigated individual-level co-occurring barriers to ART adherence to identify subgroups of individuals who may benefit from a focused intervention based on their common characteristics. As a result, three distinct subgroups emerged. The most prevalent group reported few barriers to pill-taking other than occasionally forgetting or others being around, a second smaller group reported feeling too sick to take ART as their only barrier, and a third small group reported multiple barriers to adherence. Findings suggest that forgetfulness and others being around are the most common reasons for missing doses, in line with previous research among adolescents and adults (Denison et al., 2015; Sphiwe Madiba & Josiah, 2019; Murphy, 2003; Mutwa et al., 2013; Saberi et al., 2015). However, forgetfulness alone may not predict poor self-management or sub-optimal adherence. Instead, adolescents who report multiple barriers to adherence, especially concerns about side effects and medication efficacy, are at much higher risk for poor adherence.

While not a novel finding (Young, Wheeler, McCoy, & Weiser, 2014), food insecurity was associated with harmful outcomes in all three studies, emphasizing the pervasive effect of poverty on the health and wellbeing of vulnerable youth. Economic challenges associated with HIV/AIDS are well documented in the literature, with poverty contributing to increased risk for HIV and HIV increasing risk for poverty (Adejumo et al., 2015; Ssewamala et al., 2020). Nonetheless, these findings add to the evidence base for structural and economic factors linked to poor adherence in sub-Saharan Africa (Adejumo et al., 2015; Hudelson & Cluver, 2015). These findings are especially salient given that food insecurity among people living with HIV increased with the Covid-19

pandemic (UNAIDS, 2022b), including within this sample (Thurman, Zani, Lockett, Nice, & Sampson, 2023). In particular, adolescent girls and women face a global nutrition crisis (UNAIDS, 2022b; UNICEF, 2023).

## IMPLICATIONS

These findings have important implications for intervention development to minimize stigma and improve ART adherence among vulnerable youth.

1. First, broader community stigma reduction efforts are urgently needed, especially in the school, peer and healthcare environments where adolescents living with HIV interact. Addressing the drivers of stigma may prevent its application and subsequent harm (UNAIDS, 2020a). Indeed, recent experiences of mistreatment due to HIV status were common among this sample and associated with adverse outcomes, including HIV-related shame, depressive symptomology and anxiety and lower ART adherence. However, rigorous evidence is lacking for community-level HIV stigma-reduction interventions (Andersson 2020; Stangl 2013; Smith 2020), particularly among adolescents (Gavan et al., 2022; Hartog et al., 2020).
2. Second, in the face of persistent experiences of stigma and psychological distress symptomology presented in this study, adolescents would benefit from additional support managing their mental health (Cluver et al., 2022). During adolescence, peers are an important source of emotional support (Woolfolk & Perry, 2015), yet findings from this thesis suggest that adolescents living with HIV cannot disclose their status indiscriminately. Thus, they may need additional support in more secure social networks, such as clinic-based peer support groups (Mavhu et al., 2020; Woollett et al.,

2021; Zandoni et al., 2019) and households bolstered by family-centered programming (Bhana et al., 2014). Further, the extent to which acts of HIV-related mistreatment are internalized (e.g., impact intrapersonal cognitions and affect) likely varies by individual factors and circumstances (e.g., positive or negative coping skills or availability of social support) (Fazeli et al., 2017; Turan et al., 2016), which were not measured in this thesis. While the evidence base for internalized stigma reduction interventions for people living with HIV is small, and youth remain under-represented in research (Pantelic et al., 2019), psychological support and cognitive behavioral therapy have shown promising results among South African women (Peltzer et al., 2017; Tshabalala & Visser, 2011). In addition, interventions that include structural components are more effective (Pantelic et al., 2019).

3. Third, adolescents need support to manage their physical health, including HIV and ART-associated illness and side effects, to avoid deductive disclosure and minimize barriers to daily pill-taking. The physical health of adolescents with perinatally acquired HIV may be particularly challenging to manage given the long-term health consequences of HIV disease, including non-AIDS morbidities such as central nervous system abnormalities, cardiovascular disease risk, bone loss, and renal dysfunction (Deeks, Lewin, & Havlir, 2013; Hazra et al., 2010). Further, ART use is associated with short and long-term toxicities that vary by drug and have a cumulative impact over time (Deeks et al., 2015). Prior research suggests that experiencing multiple side effects is common among adolescents in South Africa (Natukunda et al., 2017), many of whom are not yet on the recommended first-line dolutegravir regimen (Elashi & van Wyk, 2022; Mabizela & Van Wyk, 2022; Natukunda et al., 2017). Correct weight-

- based dosing is challenging during adolescence, given frequent growth spurts, and there is an increased risk of drug toxicity if not properly transitioned from higher pediatric dosing to lower adult dosing (Rakhmanina & Phelps, 2012).
4. Next, food insecurity and health-system-related barriers should be addressed to improve adolescent outcomes. While there is limited evidence on the effectiveness of service delivery interventions to support adolescents' linkage from HIV diagnosis to treatment initiation, retention and adherence, increasing clinic accessibility and adolescent-tailored services appear essential (Cluver et al., 2018; MacPherson et al., 2015). Additionally, targeted intervention via cash grants and social protection interventions, such as food parcels and clinic transport subsidies, may improve retention in care (Cluver et al., 2016; Fahey et al., 2019; Fahey et al., 2020; McCoy et al., 2017).
  5. Finally, findings from the three studies in this thesis demonstrate that factors at multiple levels and from many domains influence adolescent ART adherence. Community-based approaches, including home visits from patient advocates, may hold particular promise to address the multi-faceted factors affecting adolescent adherence; however, their effectiveness has not been evaluated explicitly among adolescents using rigorous study designs (Fatti et al., 2016; Fatti et al., 2014; Grimwood et al., 2012; Igumbor et al., 2011).

## STRENGTHS AND LIMITATIONS

This study reached a large community-based sample of adolescents living with HIV in a high HIV prevalence setting, enhancing the generalizability of findings beyond clinical

populations. However, the strength of these findings should be assessed with the following limitations in mind.

The survey instrument was designed to be brief and uncomplicated so adolescents could complete it within the one-hour Vhutshilo 3 session. As a result, the survey often only included single items from validated scales. In particular, the lack of complete and comprehensive stigma measures is a significant limitation of this study, given the focus on various dimensions of stigma and the need for robust, standardized measures to facilitate comparability with other studies (Turan, Hatcher, et al., 2017). Further, many critical individual characteristics that influence HIV management were not measured in the survey, potentially confounding results. For example, orphanhood status, mode of HIV transmission, time on ART, and ART regimen may be important (Chandwani et al., 2012; Ferrand et al., 2016; Hendrickson et al., 2019; Idele et al., 2014; Sherr et al., 2018; Slogrove & Sohn, 2018) (Hudelson & Cluver, 2015; Natukunda et al., 2017). The self-administered nature of the survey also resulted in missing and sometimes inconsistent data, which might have been avoided with a different survey modality (Fowler, 2008). Missing data is common in HIV research with one review finding the average percentage of missing values was 26% across studies (Harel, Pellowski, & Kalichman, 2012). In contrast, the total number of cases missing values was lower across the three studies in this thesis (7-12%) and sensitivity analyses indicated selection bias was likely minimal. In addition, minimum sample sizes based on *a priori* power calculations were met despite the reduced analytic population.



All outcomes in this study were self-reported. The reliance on self-reported ART adherence for outcome ascertainment risks incomplete data and misclassification of the outcome and would be improved by more direct measures of ART adherence, such as viral load results. Qualitative research in the Eastern Cape highlighted the difficulties faced by adolescents living with HIV in recalling and relating their adherence practices precisely (Hodes, Cluver, Toska, & Vale, 2018). Adherence reports from adolescents, caregivers, and health workers were often inconsistent and incomplete. In addition, it was challenging for adolescents to openly convey adherence practices for fear of rebuke and the desire to be ideal patients. While adolescents in this study completed their surveys anonymously, they may have felt similar pressures given the support group context. Non-judgmental phrasing was used to help minimize their concerns in this regard (Hodes et al., 2018).

On the other hand, multiple studies have found correlations between self-reported ART adherence and viral suppression (Cluver et al., 2018; Usitalo et al., 2014). Further, a simple self-reported measure may be a valuable and efficient tool when more complex or expensive methods cannot be used (Wilson et al., 2016), as in this survey implemented during routine program operations. However, self-reported adherence measures are not without limitations, including social desirability and recall bias, question misinterpretation, and ceiling effects (Phillips et al., 2017), and are still considered inferior to pharmacy refill and medication event monitoring systems (MEMS) in their ability to explain virologic outcomes (Bezabhe et al., 2016). In addition, a previous validation study found that the 'days missed' item used in this study may overestimate adherence (Wilson et al., 2016).

The ART adherence outcome in this study was dichotomized at a threshold of 90%, as opposed to the more common 95% (Paterson et al., 2000). This lower threshold was selected based on multiple recent reviews which suggest viral suppression may be achieved at lower levels of adherence based on improved ART treatment regimens (Bezabhe et al., 2016; Byrd et al., 2019; Kahana et al., 2013). For example, a 2020 study found that both INSTI-based and NNRTI-based regimens achieved viral suppression with adherence levels as low as 75% and 78%, respectively, suggesting that some regimen types may allow more missed doses than others (Byrd et al., 2019). Further, two meta-analyses, including one focused on children and adolescents, found no significant group differences in virologic outcomes between different thresholds of good adherence (e.g., “perfect” (100%), “near perfect” ( $\geq 95\%$ ) and “good enough” ( $\geq 80\text{--}90\%$ ) adherence) (Bezabhe et al., 2016; Kahana et al., 2013). The current first-line ART regimen for adolescents in South Africa contains Dolutegravir [DTG], an integrase strand transfer inhibitor (INSTI) (NDoH, 2020), which has a higher potency and barrier to developing resistance than preceding medication groups, even with incomplete adherence (Parietti et al., 2021). However, the scale-up of INSTI-based regimens is incomplete (Natukunda et al., 2017) and using a 90% threshold does not imply that efforts to improve adherence should stop there.

The validity and reliability of psychometric survey instruments may also contribute to misclassifying exposure status. While research supports the underlying universality of the experience of depression and anxiety (Sweetland et al., 2014), there is a dearth of validated tools, particularly for use in child and adolescent mental health (Ali et al., 2016). To minimize the potential for bias, this study prioritized anxiety and depressive symptomology

instruments with a previous history of use among adolescents living with HIV in South Africa (Boyes et al., 2019; Cluver et al., 2013; Woollett et al., 2017).

The use of convenience sampling undermines the generalizability of findings from the sample to the whole population of adolescents living with HIV, and results may be difficult to replicate in other populations. In particular, the *Data integration to improve youth outcomes study* focused on urban settings in Gauteng and KwaZulu-Natal provinces and is not generalizable to all settings in South Africa. However, these settings encompass South African areas with the highest number and prevalence of adolescents living with HIV. Further, adolescents were recruited to participate in the survey from peer support groups provided by community-based organizations, extending generalizability beyond clinical samples (Hodes et al., 2018). However, they may differ systematically from youth who choose not to or cannot participate in structured interventions offered by community-based organizations. Further, the deviation from probability sampling affects estimates of sampling error (Fowler, 2008). Clustering by group was accounted for in analyses with a mixed effects model, but additional adjustments for the probability of selection were not made.

Finally, as addressed in all three papers, the cross-sectional design limits causal inference into the relationships between the predictors and outcomes of interest. However, rather than establish causal associations, we aimed to explore possible associations between various risk factors and ART adherence to inform current programming and future research efforts. Therefore, future studies should employ longitudinal data study designs and

sequential mediation analyses to rule out reverse causation and better capture adherence dynamics over time (Zhou et al., 2021). Nonetheless, cross-sectional data helps generate more immediate results to guide intervention development.

## CONCLUSION AND RECOMMENDATIONS

Efforts to improve the 95-95-95 treatment cascade and end AIDS as a public health threat will yield limited long-term success if young people cannot stay in care and adhere to a life-long medication regimen. Given their critical developmental stage, the challenges of ART management are especially complex, and the price of failure is extraordinarily high. Thus, knowledge that can directly inform intervention development for improving adolescent outcomes is critical (Armstrong et al., 2018a). In particular, few effective interventions exist to improve adolescent ART adherence (Ridgeway et al., 2018) or address HIV-related stigma among adolescents living with HIV (Hartog et al., 2020).

These findings provide insight into potential intervention foci among adolescents in high-prevalence HIV settings willing and able to engage in community-based programming. Managing physical health, including opportunistic infections, non-AIDS morbidity and side effects, and addressing psychological well-being, including anxiety and disclosure concerns, may reduce experiences of HIV-related mistreatment and improve ART adherence. Further, programming should attend to the contextual realities of adolescents living with HIV in which food insecurity undermines positive outcomes.

Interventional research is needed to bridge research gaps and inform targeted interventions to improve adolescent outcomes (Armstrong et al., 2018b). Future research should build on the findings from this thesis with longitudinal mediation study designs to better establish the temporal relationship and plausible causal pathway between intentional and deductive disclosure, different dimensions of stigma, psychological distress and ART adherence among adolescents and young adults. Doing so can inform the design and evaluation of the complex, multi-component interventions likely necessary to reduce stigma and improve HIV treatment outcomes (Bryan et al., 2007; Pantelic et al., 2019). Where feasible, samples should be probability-based to minimize selection bias and improve generalizability and should be large enough to allow for subgroup analysis by potentially important characteristics, such as age, gender, and mode of HIV transmission. In particular, young adults (ages 20-24) are understudied (Kim et al., 2014). In addition, multiple ART adherence recall strategies and timelines should be captured to construct better adherence metrics (Hodes et al., 2018), and viral load should be measured to objectively quantify the therapeutic response. Finally, protective factors and resilience measures, such as social support and adaptive coping, should be included to further inform interventions designed to buffer adolescents from the adverse effects of poverty and stigma and reduce disparities in HIV treatment outcomes (Earnshaw, Bogart, Dovidio, & Williams, 2013; Skovdal, 2012).

## APPENDIX 1. OPERATIONAL DEFINITIONS

**Children, Adolescents, Youth & Young People:** Per UNAIDS guidance, ‘children’ are defined as persons below age 18, ‘adolescents’ are aged 10 to 19 years, and ‘youth’ are between the ages of 15 and 24 years (UNAIDS, 2016). The term ‘young people’ encompasses adolescents and youth (i.e., 10-24 years). However, in recognition of the protracted growth of reproductive, musculoskeletal, neurodevelopmental, endocrine, metabolic, immune, and cardio-metabolic systems extending into young adulthood, adolescence may be best considered 10-24 years (Sawyer, Azzopardi, Wickremarathne, & Patton, 2018). Thus, this prospectus uses the terms ‘adolescents’ and ‘young people’ interchangeably and gives attention to specific age disaggregates (e.g., 10-14, 15-19, 20-24) where available.

**Orphans:** Orphans are children (0-17 years) who have lost one or both parents. They may be further classified as maternal, paternal, or double orphans depending on which parent/s are deceased.

**Orphans and vulnerable children, adolescents and young adults:** Orphans and vulnerable children, adolescents and young adults (OVCA&Y), as defined by PEPFAR and USAID’s OVCA&Y programs, consist of children and youth in a range of adverse situations, including children/youth living with HIV, living with caregivers who are living with HIV, orphaned, at risk of acquiring HIV, or a combination of these factors (USAID, 2021).

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