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The Association Between Neighborhood-level Poverty and HIV Virologic Failure Differs by Gender in Durban, South Africa: A Multi-level Analysis

By

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Master of Public Health

Global Epidemiology

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B.A., University of California, Berkeley, 2012

Thesis Committee Chair: Michael Kramer, PhD

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An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

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Abstract

The Association Between Neighborhood-level Poverty and HIV Virologic Failure Differs by Gender in Durban, South Africa: A Multi-level Analysis

By Daniella Coker

Objective

If left inadequately diagnosed or untreated, HIV virologic failure (VF) can lead to acquired drug resistance or early mortality. Gender differences in predictive risk factors for VF, such as individual-level socioeconomic status (SES), have been found. In order to characterize the mechanisms through which SES impacts VF, it is important to also consider the role of neighborhood-level SES.

Methods

This is a secondary analysis of the Risk Factors for Virologic Failure (RFVF) case-control study of HIV positive patients residing in eThekwini and attending McCord Hospital in Durban, South Africa between October 2010 and June 2012, after at least 5 months of their first ART regimen. Cases were those with virologic failure (VL > 1,000 copies/mL) and controls were those without virologic failure (VL ≤ 1,000 copies/mL). Multilevel logistic regression (GEE) models incorporating interaction by gender were used to assess the gender-specific associations between neighborhood-level poverty and VF after controlling for individual-level demographic, clinical, and SES factors.

Results

152 cases and 286 controls representing 52 neighborhoods (Main Places) were included in this analysis. Most patients in the sample were female (64.6%), came from high poverty neighborhoods (60.7%), were employed (72.4%), and had at least some secondary-level education (80.6%). In a GEE model only containing gender, neighborhood-level poverty, and their interaction term (Model 1) the OR for the effect of residence in low versus high poverty neighborhoods for men was 1.42 (95% CI: 0.79, 2.53) and for women was 0.76 (95% CI: 0.48, 1.22). Adjusting for individual-SES and clinical factors (Model 3: OR_{men} = 1.23; 95%CI = 0.63, 2.43 and OR_{women} = 0.75; 95%CI = 0.49, 1.15) provided similar results for both men and women compared to when only CD4 count was adjusted for (Model 4: OR_{men} = 1.28; 95%CI = 0.64, 2.55 and OR_{women} = 0.74; 95%CI = 0.48, 1.16).

Conclusions

After controlling for individual-level socioeconomic (SES) and clinical factors, men living in richer areas and women living in poorer areas had greater tendency for VF, perhaps partly due to gender-specific HIV-related stigma. Future studies should employ mediation analyses to further characterize potential mechanisms through which neighborhood- level SES effects may impact VF differently for men and women.

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Chapter I: Background/Literature Review

Introduction

South Africa has more people living with HIV than any other country in the world. Despite a substantial increase in access to antiretroviral therapy (ART) in Sub-Saharan Africa, continued success of ART depends on effective monitoring and management of patients with virologic failure (VF). VF is often a precursor to HIV drug resistance, which presents additional challenges to HIV care. While individual-level risk factors of VF have been identified, less is known about how the characteristics of the social and physical environment may impact VF. Furthermore, even though it has been indicated that men and women may have different experiences regarding VF and its risk factors, even less is known about how characteristics of the social and physical environment may impact VF differently for men and for women. A greater understanding of the role of neighborhood-level factors can shed light into the mechanisms that lead to VF and provide important information for targeting community-level interventions.

The Risk Factors for Virologic Failure and HIV-1 Drug Resistance in Durban study (RFVF) is a case control study (with density sampling of controls) conducted at McCord Hospital in Durban, South Africa. The purpose of the study was to identify predictors of virologic failure and drug resistance in HIV-positive patients and to study the emergence of HIV drug resistant mutations in this setting. This and subsequent analyses of RFVF data identified various individual-level socioeconomic (SES) risk factors for VF that differed by gender. In order to further investigate whether neighborhood-level SES had an effect on VF above and beyond that of individual-level SES, multi-level generalized estimating equation (GEE) logistic regression models of neighborhood-level poverty were created in this sub-study.

HIV in South Africa

HIV Epidemiology

With over 5.6 million people living with HIV, South Africa has more people living with HIV than any other country in the world [1]. South Africa is one of the countries most impacted by the global HIV epidemic, where the prevalence of HIV among adults aged 15-49 years is approximated at 15.9% [2]. More women than men are living with HIV, accounting for an estimated 62% of cases and a prevalence of 17.4% among women ages 15-49 years old [2, 3]. In 2012, women had nearly twice the HIV incidence than males, with an estimated 2.3% incidence rate and 251,000 new cases that year [4]. Despite stabilization in the number of new HIV infections per year, there remains an increasing prevalence of HIV in the country as antiretroviral therapy (ART) has allowed people with HIV to live longer. HIV cause-specific mortality is also of great concern in South Africa, where there were 627 HIV related deaths, per 100,000 population, in 2009. It was estimated in 2013 that 200,000 deaths due to AIDS occur each year in the country [5, 6].

The province of KwaZulu-Natal on the eastern coast of the country remains at the epicenter of the HIV epidemic [7]. According to the South African National HIV survey of 2012, the prevalence of HIV among 15-49 year olds has increased from 15.7% in 2002 to 27.9% in 2012, which represents the highest prevalence of any other province in South Africa [4]. HIV prevalence in KwaZulu-Natal can be as high as 40% among women attending antenatal clinics [7]. Within the KwaZulu-Natal province, the eThekwini metropolitan area has an HIV prevalence of 14.5%, which is higher than the South African national prevalence rate [4].

Development of the HIV epidemic in South Africa

During the early years of the epidemic, HIV primarily affected homosexuals and hemophiliacs who had received blood transfusions [7, 8]. Starting in 1988 there was a gradual introduction of HIV into the black heterosexual community, primarily fueled by the circular migration system that formed the backbone of the political economy in apartheid South Africa [7]. In order to make a sufficient living, many men left their rural homes to work in the urban mines or factories, migrating back to their families a few times a year. The transient and increasingly sexually active lifestyles of many of these circular migrant workers played a role in spreading HIV across social networks in South Africa. Between 1990 and 1994, HIV prevalence began to grow exponentially, particularly among heterosexuals [7]. There were also dramatic increases in the number of HIV infections among pregnant women (0.8% to 7.6%), which frequently led to perinatal infections [7].

HIV denialism propagated by the highest levels of government also fueled the epidemic, with an estimated, “330,000 South Africans dying earlier than necessary from AIDS and over 35,000 babies [becoming] needlessly HIV infected” [9, 10]. However, the introduction of the US President’s Emergency Plan for AIDS Relief (PEPFAR) in 2003, the support from the Global Fund, World Bank and other multi-national partners, and the formation of the Treatment Action Campaign, assisted in increasing availability of HIV and decreasing incidence rates [7].

HIV Treatment

Given the efficacy of antiretroviral therapy (ART) in reducing both AIDS deaths and HIV transmission, increasing access to ART has become a priority for many countries affected by the HIV epidemic [11, 12]. Data from over 37,000 HIV-positive adults initiating ART for the first time showed a near-normal life expectancy provided that ART was started before CD4 count dropped below 200 cells/uL [13]. Rodger et. al’s prospective study also found that while mortality rate was higher among those with CD4 count of less than 500 cells/uL (SMR 1.77, 95% CI: 1.17, 2.55), those with CD4 count greater than 500 cells/uL experienced no difference in mortality rate than that of the general population (SM 1.00, 95% CI: 0.69, 1.40) [14]. In 2003, the South African government announced the implementation of a five-year ART rollout plan to increase access to ART for the country's HIV infected population [15]. Starting in 2004, the South African government began collaborating with the United States President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis, and Malaria, which led to increased access of antiretroviral therapy (ART) and other HIV treatment and prevention services [16-18]. Prior to the national roll-out, availability of ART was mostly limited to the private sector and research studies. However, by 2009, the number of PEPFAR-supported HIV facilities increased from 184 to over 1,400. During the same time period there was also an increase in the number of patients receiving ART per site, which increased from a median of 81 patients in 2005 to 136 patients in 2009 [17]. By the end of 2012, 2.3 million people were being initiated on ART and HIV treatment coverage had reached 83% coverage according to WHO 2010 treatment guidelines [19-21]. Despite the improvements in ART access, as of 2011 only 37% of South Africans with advanced HIV infection were covered by ART [5].

In accordance with international recommendations, the Southern African HIV Clinicians Society recommends the use of a non-nucleoside transcriptase inhibitor (NNRTI) + 2 nucleoside reverse transcriptase inhibitors (NRTIs) as the first-line ART regimen for previously untreated patients [22]. While efavirenz (EFV) is the preferred NNRTI, nevirapine (NVP) may be used when contraindications prevent use of EFV [22]. The favored 2-NRTI combinations for use are lamivudine (3TC) + tenofovir (TDF) or emtricitabine (FTC) + TDF [22].

According to newly updated national guidelines, individuals for whom ART commencement is recommended include the following [23]:

1. CD4 count drops below 500 cells/uL

2. Irrespective of CD4 count, WHO clinical stage 3 and 4, other severe HIV-related disorders (immune thrombocytopenia, thrombotic thrombocytopenic purpura, polymyositis, lymphocytic interstitial pneumonitis), non HIV-related disorders

(malignancies, hepatitis B, hepatitis C), and any condition that requires long-term immunosuppressive therapy.

For those HIV-infected individuals in a serodiscordant relationship, in addition to ART commencement it is recommended that both partners discuss safe sex practices [22]. ART should be deferred until patients have a full understanding of the therapy process and the importance of 100% adherence, but not deferred so long as to result in clinical deterioration or death [22]. Studies have shown that at least three fully active ART drugs are necessary treatment success and prevention of acquired drug resistance [24].

If an individual must be switched to second-line treatment options, due to toxicity or treatment failure from a first-line regimen, the appropriate treatment options are as follows:

1. If the patient failed on an AZT-based first-line therapy, TDF with 3TC, or LPV/r is recommended

2. If the patient failed on a TDF-based first-line therapy, AZT with 3TC and LPV/r is recommended [25].

With the success of ART, HIV has become a chronic disease that requires lifelong therapy. The rapid increase in the availability of ART in Sub-Saharan Africa has allowed many South Africans to also reap the benefits of lifelong HIV treatment. However, as ART availability and the number of individuals living with HIV continue to increase, the proportion of patients for whom it is difficult to retain in care will also likely increase, creating additional challenges for timely identification and management of treatment failure [16, 26].

Virologic Failure (VF)

An individual must have been taking ART for at least 6 months before it can be determined that a treatment regimen has failed [27]. In 2010, the WHO defined three different measures of HIV treatment failure as follows:

1. Virologic failure: Plasma viral load above 1,000 copies/mL based on two consecutive viral load measurements 3 months apart

2. Immunological failure: CD4 count falls to or below the baseline, or persistent CD4 counts below 100 cells/mm^3

3. Clinical failure: New or recurrent clinical event indicating severe immunodeficiency (defined as WHO clinical stage 4) after 6 months of effective treatment [27].

Virologic failure occurs when an ART regimen is unable to maintain maximum virologic suppression and HIV viral replication rebounds, resulting in a loss of the clinical benefits obtained through ART [28]. Virologic failure occurs first, followed by immunological failure and then clinical failure [27]. There is an increasing amount of evidence suggesting that using clinical symptoms to identify treatment failure may lead to misclassification of said treatment failure [29, 30]. False negatives can lead to untimely switching to second-line ART and increased drug resistance, morbidity, and mortality. False positives can lead to unnecessary switching to a second-line ART, which may be a final treatment option in many resource-limited settings [29, 31]. Thus assessment of virologic failure through viral load testing in conjunction with CD4 count is becoming the preferred indicator of treatment failure [27, 32].

The above definition of virologic failure is primarily based on two sources of evidence. First, even though viral blips, or intermittent low-level viraemia (at 50 – 1,000 copies/mL), may occur during effective treatment, these blips are not associated with elevated risk of treatment failure unless low-level viraemia is maintained. Second, the literature has shown that HIV transmission risk and disease progression is minimal when viral load is maintained under 1,000 copies/mL [27]. The optimal threshold for defining virologic failure and thus switching ART treatments has yet to be established. Nevertheless, the 2010 WHO guidelines for monitoring response to ART recommend to commence viral load testing for a patient when a viral load threshold is above 1,000 copies/mL, and to switch to second-line ART if a repeat measure is above 5,000 copies/mL [27].

According to a systematic review of 19 studies of virologic failure (defined as viral load greater than 1,000 copies/mL) of patients on first-line ART for between 3 to 48 months, virologic failure prevalence is approximately 15% [33]. Prevalence of virologic failure on second-line ART, however, tends to be higher than that of first-line ART. In a cohort patients with a single episode of virologic failure in KwaZulu-Natal, 30% percent of participants did not obtain virologic suppression of less than 400 copies/mL after 24 weeks on second-line ART [34]. Other South African studies have indicated prevalence of virologic failure from second-line ART as high as 40% [34, 35].

Continuing a failing regimen on which virologic failure was identified is associated with adverse outcomes, such as increased morbidity and mortality. In an analysis by Petersen et. al using prospective data, it was shown that delay until treatment modification of patients with virologic failure was associated with an increased hazard of all-cause mortality, after controlling for time-dependent confounding [36]. In a subsequent study, Petersen et. al examined HIV-positive patients from four cohorts from Uganda and South Africa with virologic failure whose first-line therapy were NNRTI-based regimens, and found a higher adjusted mortality among those who did not modify regimens compared to those who had [36].

Acquired Drug Resistance: Effect of Virologic Failure (VF)

Continuing a failing regimen on which virologic failure was identified may also select for drug resistant HIV-1 (acquired drug resistance) [33]. Acquired drug resistance is said to occur when viral suppression is not completely achieved and drug resistance-related mutations develop as viral replication continues at low levels [37]. This is contrasted with transmitted drug resistance, which refers to when an individual is infected by HIV-1 viruses already containing resistance mutations [37]. Studies have shown a temporal link between virologic failure and acquired drug resistance mutations. For instance, a cohort study in KwaZulu-Natal followed 141 patients with virologic failure, and after 24 weeks of follow-up, at least one major resistance mutation was found in 87% of patients [34]. In Marconi et. al.'s study, patients having failed their first highly active antiretroviral therapy (HAART) regimen in KwaZulu-Natal were followed from January 2005 through August 2006. By the end of the study period, 83.5% of participants had at least one drug resistance mutation, 64.3% had resistance mutations to at least one drug in two classes, and 2.6% had resistance mutations to at least one drug in three classes [38]. A series of WHO surveys of acquired resistance estimate that 72% of patients who fail therapy after 12 months on ART have drug resistance [39]. Similarly, Aghokeng et. al. examined the virologic outcomes and drug resistance mutations of HIV-infected patients in Cameroon after 36 months on first-line ART regimens. Of the 66 patients who experienced virologic failure in the study, 81.5% carried a drug resistant virus, with a high proportion of those having developed drug resistance during treatment [40].

The development of acquired drug resistance during first-line therapy may depend on the type of drug used. According to a systematic review of acquired and transmitted drug resistance in Africa between 2001 and 2011, the pooled prevalence of drug resistance mutations in Africa was 10.6%, with protease inhibitor mutations most highly represented in Southern Africa [41]. Several other studies have implied a greater association between drug resistance and NNRTIs, compared to other ART drugs. For instance, the PharmAccess African Studies to Evaluate

Resistance Monitoring cohort of 2,436 ART-naïve individuals representing 11 geographic areas in Africa reported drug class-specific resistance prevalence of: 3.3% for NNRTIs, 2.5% for NRTIs, 1.3% for ritonavir-boosted protease inhibitors (bPIs), and 1.2% for dual-class resistance to NNRTIs and NRTIs [39, 42]. In Marconi et. al.'s study of patients who failed their first HAART regimen in KwaZulu-Natal, it was found that the most common types of drug resistance mutations were associated with NNRTIs and NRTIs [38].

Acquired drug resistance can lead to a host of problems, such as limited and often poorly tolerated, expensive treatment options, spread to newly infected individuals, and a potentially greater risk of mortality [28, 39, 43]. For example, Hogg et. al. characterized the risk factors of mortality among patients first starting ART in a 5-year cohort study. The study showed that those who acquired drug resistance were more likely to have died during the study period compared to those without acquired drug resistance (Hazard ratio: 1.75, 95% CI: 1.27, 2.43) [43]. Unfortunately, comprehensive global assessments have estimated an annual increase in resistance prevalence of 14% in sub-Saharan Africa since the ART roll-out [39]. Local studies in South Africa have shown that while mutations for HIV-1 transmitted drug resistance (TDR) were most often associated with NNRTI, TDR has remained < 5% (WHO low-level threshold) since 2002 [44]. The issue of emerging HIV drug resistance has influenced the development of early warning indicators (EWIs) as part a WHO-led public health strategy to minimize and assess HIV drug resistance, particularly in countries scaling up ART. The program identified five indicators of importance for monitoring HIV drug resistance, one of which is successful viral load suppression at 12 months on a first regimen of ART [45]. The clinical complications associated with drug resistant HIV-1 highlights the importance of successful monitoring and prevention of virologic failure.

It is important to distinguish between drug resistant and non-drug resistant cases of VF, as second-line ART regimens are costly and less accessible, especially in low- and middle-income countries, and can increase unnecessary toxicity for such patients. While acquired drug resistance is often a consequence of virologic failure, it may occur in the absence of drug resistance. In an analysis by Johnston et. al., it was found that among a cohort of 417 HIV patients switching to second-line ART, more patients with optimal adherence had ART resistance mutations than those with suboptimal adherence. Furthermore, it was the absence of ART resistance mutations and poor adherence pre-switch that were associated with virologic failure after switch [46]. Another study has shown that also, somewhat paradoxically, individuals without drug resistance tended to have greater mortality than those with [34]. These results suggest that it is poor adherence (and perhaps the psychosocial reasons related to poor adherence) that are major drivers of virologic failure rather than solely drug resistance.

Poor Adherence: Cause of Virologic Failure

Optimal adherence to an ART regimen is a key predictor of HIV health outcomes [47]. Among the most common reasons for treatment failure, as cited by the Southern African HIV Clinicians Society include: transmitted drug resistance, previous use of a single-dose of NVP for prevention of mother-to-child transmission (PMTCT) interactions of drugs that decrease ART concentrations, and inadequate patient adherence [48]. Research indicates that consistent high levels of adherence are necessary in order for successful viral suppression [49-53] and prevention of acquired drug resistance [54-57], disease progression [58], and death [59].

However, the level of adherence needed to maintain virologic suppression may decrease with longer time spent on a successful ART regimen [60]. For instance, among HIV-positive individuals who maintained at least 50% adherence on NNRTI-based ART regimens, the probability of virologic failure was significantly lower after 12 months of continuous viral suppression compared to those after only 1 month of continuous viral suppression [60]. The degree of adherence needed to maintain virologic suppression has also been shown to differ between antiretroviral regimens and the pharmacokinetics of the individual antiretrovirals in the regimen. Therefore, while poor adherence may not always lead to virologic failure in every individual, the best practice is to promote 100% adherence amongst all HIV patients on ART.

An increasingly popular measure of medication adherence is Medicine Possession Ratio (MPR), which estimates adherence by the number of daily doses of ART drug provided and the number of follow-up days since ART initiation [51]. In Minga et. al.'s prospective cohort study of HIV-infected adults in Cote d'Ivoire, after 12 months of first-line ART, 85% of patients with MPR < 50% had detectable HIV-1 viral loads and 37% had at least 1 resistance mutation after 12 months of first-line ART, compared 9% and 4% respectively in patients with MPR > 95% [51, 61] Hassan et. al. found that participants with 'unsatisfactory' adherence, defined as MPR < 95%, in a rural HIV clinic in Kenya had a statistically significantly higher prevalence of acquired HIV drug resistance than those with 'satisfactory' adherence, defined as MPR ≥ 95% (frequency [%]: 12 [27.9] vs 17 [9.5], p = 0.004) [62].

With regards to acquired drug resistance, it is thus suboptimal adherence rather than complete non-adherence that tends to lead to acquired drug resistance. For instance, in a study of HIV treatment outcomes in Tanzania, it was found that incomplete adherence to ART was associated with nearly a three-fold increase in the odds of VF [63].

Despite the benefits of optimal adherence, non-adherence to ART in adult populations ranges from 33% - 88% in a variety of settings [64]. Non-adherence in South Africa has been estimated between 10% and 37% [65-68]. While some have claimed that optimal adherence is not possible in areas of low socioeconomic status, studies in Uganda, Senegal, and South Africa have shown high levels (> 95%) of ART adherence [68-71]. A meta-analysis of ART adherence studies estimated that 77% of the African population was achieving adequate levels of adherence [47]. Yet, many of these studies were conducted in urban, well-resourced areas, where economic and transportation factors may not impact adherence as negatively as they may in rural, poorly-resourced areas. Thus, there is a need for continued improvement of access and adherence support to reduce the risk of adverse HIV health outcomes.

Maintaining optimal adherence to ART may be complicated by a multitude of challenges. For some, aspects of the pharmacological regimens deter adherence. Many of these regimens include taking numerous pills per day, each of which must be coordinated around dietary restrictions, certain timings around meals, and may be accompanied by negative tastes and side effects [72, 73]. Many studies on adherence cite reasons such as forgetting or being away from home as reasons for not adhering to ART, likely compounded by the requirements of the various regimens [74]. Others cite disease-related and individual-related factors as potential contributors to ART non-adherence, despite the at times inconsistent findings in the literature [75]. Among those patient-related factors, the role of socioeconomic status is of particular interest for this analysis.

Risk Factors for Virologic Failure

The detrimental health consequences of virologic failure (VF) have motivated research into risk factors for predicting VF within individuals. The development of a set of individual-level risk factors would be particularly useful to clinicians for early identification of patients most at risk for VF. Previous studies have explored and identified demographic, clinical, psychosocial, transportation, and socioeconomic factors that may contribute to improved screening and management of patients with VF [26].

Demographic risk factors: Gender and Age

The associations between gender, age, and HIV treatment outcomes have been established in the literature. Many studies have shown that men in particular have greater mortality rates, greater loss to follow up, and less HIV virologic suppression than women. A systematic review and meta-analysis showed that among ART enrollees in Africa, the risk of death among men were significantly higher than the risk of death among women [76]. One study which compared mortality rates among HIV positive patients initiating ART with non-HIV related mortality rates in South Africa and three other sub-Saharan countries used multivariable models to show that even after controlling for variation in background mortality, females had a 20% lower risk of death compared to males [77]. Several African studies have also shown significant gender differences in virologic failure. A retrospective cohort study in rural South Africa found that male gender was significantly associated with virologic failure in both univariate and multivariate analyses [78] . A study in western Uganda examined 305 persons living with HIV and receiving ART for gender differences in ART outcomes and found that after six months of treatment, females were more likely to have viral suppression (defined as a viral load of > 400 copies/mL) as compared to males (OR 2.14, 95% CI: 0.99, 4.63), after controlling for age, marital status, education, occupation, and baseline CD4 count [79].

One potential explanation for the gender differences observed in many HIV treatment outcomes is that ART access and adherence interferes with the ideals of masculinity that prevail in many cultures. Inherent to the concept of masculinity are qualities of toughness and fearlessness, which studies have suggested manifest as perception of HIV as a threat to men's masculinity and subsequently accessing ART later in the progression of disease, which can increase likelihood of treatment failure [80, 81]. This conceptual framework is supported by Hare et. al's analysis of gender specific risk factors for HIV virologic failure among HIV positive patients in the RFVF study. It was found that when restricted to males, among the most significant individual predictor of HIV virologic failure was car ownership, which can be considered a mark of social status and a means of providing for family [16].

Other explanations for the gender disparity in HIV treatment outcomes could be attributed to other experiential differences between the lives of men and women in Africa. For instance, increased access for women to ART may in part be attributed to the fact that many HIV health services in Africa are provided through maternal and child health services [81]. Additionally, women may also be more accustomed to adhering to regular medications (such as through the use of contraceptives), resulting in increased adherence to ART [81]. Furthermore, men have traditionally been part of migratory populations for work in mines and agriculture in South Africa. The transient and sexually active lifestyles of many migrant workers thus have likely impacted HIV infections rates, social support, and routine access and adherence to ART [82, 83].

In general, HIV treatment outcomes and adherence to ART is poorest in younger populations. A systematic review and subsequent meta-analysis of aging and adherence to ART found that older age was statistically significantly associated with a reduced risk for non-adherence to ART by 27% (RR 0.72; 95% CI: 0.64, 0.82) [84]. Similarly, a study in rural South Africa found that non-adherence to ART was highest among the 18-28 years age group, while it was the lowest in those older than 48 years of age [85]. An observational cohort study examined records from HIV positive individuals enrolled in a disease management program within nine countries in Southern Africa to compare ART adherence rates by age-specific subpopulations. At 6, 12, and 24 months after ART initiation, the adolescents (11 – 19 years old) had significantly lower adherence rates than those of adults (30 years and older), and at 12, 18, and 24 months of follow-up, the proportion of adolescents with virologic suppression was significantly lower than that of adults (e.g. between 43 – 45% compared to 60 – 62% respectively) [86]. Given many of the strict pharmacological ART regimens, the age disparity in ART adherence and virologic failure may likely be attributed to peer stigma, peer discrimination, and multiple social distractions. Yet, while older populations may experience greater adherence they may also experience significant adverse HIV treatment outcomes as a result of age-related biologic factors that negatively impact survival.

Clinical risk factors: Duration of Antiretroviral Therapy

Several studies have shown that the longer a person is on ART treatment (longer treatment duration), the less likely he/she is to experience virologic failure. For instance, in a cohort of 1,305 ART-naïve adults in British Columbia, Canada, it was found that on average the odds of viral rebound, defined as a period of virologic failure following successful virologic suppression, decreased by approximately 8% for every month of viral suppression at all tested adherence levels [87]. A second study utilized Cox proportional hazards models to determine the rate of virologic failure among nearly 2,500 patients on ART with previous virologic suppression. While 42% attained virologic failure the incidence of failure significantly decreased over time, from 33.5 / 100 person-years of follow-up at 6 months after initial suppression down to 8.6 / 100 person-years of follow-up at 2 years after initial suppression ($p < 0.0001$) [88].

Among patients who have achieved virologic suppression, previous events of virologic failure also tend to be associated with higher rates of reoccurring virologic failure. However, the results from Benzie et. al’s study in the United Kingdom also support the notion that the likelihood of viral rebound decreases with increasing duration of suppression. Among those who had failed four or more ART regimens previously, the rate of viral rebound was 32.7 / 100 person-years (95% CI: 27.6 – 37.8). However, when restricted to patients who had failed four or more ART regimens and had remained suppressed for 2-3 years and at least 4 years, the rates of viral rebound decreased to 6.3 / 100 person-years (95% CI: 3.1 – 11.2) and 1.4/100 person-years (95% CI: 0.0 – 8.1) respectively [89].

Psychosocial risk factors:

Various psychosocial factors, such as social support, stigma, substance abuse, and depression can also impact VF through their associations with medication adherence. Psychosocial barriers to optimal ART adherence may manifest in a variety of ways. For instance, social support can promote ART adherence through financial and emotional means, which can create a positive feedback loop where patients want to improve their health and adherence to maintain their social relationships [90]. Pervasive HIV-related stigma can lead to delay in disclosure and seeking care, skipping doses, social isolation, and real or anticipated rejection from family, friends, and coworkers, negatively impacting ART adherence [90-92]. Substance abuse can have severe implications on ART treatment success. Substance abuse can cause memory impairment and lack of concentration which can hinder the ability to maintain healthy lifestyle recommendations, such as medication adherence [93, 94]. Lastly, symptoms of depression include low motivation, poor concentration, and feelings of worthlessness, which can further impede the success of taking medication and attending clinic appointments for those on ART [93].

Transportation risk factors: Distance and Travel time

Longer travel times and distances are often related to travel costs, which can serve as a greater barrier to ART for individuals of lower socioeconomic status. Patients of lower socioeconomic status are often less able to travel further distances, likely due to the costs associated with such travel. In a qualitative study conducted in Uganda, it was found that even when medicines are provided free of charge, costs related to transportation as well as limited means of transportation from more remote areas were important reasons as to why some patients failed to visit their health clinic for pill refill [95]. A study of patient choice and access to HIV services in England showed that affluent patients were more likely to travel beyond their local clinics for HIV treatment compared to less affluent patients [96].

Siedner, et. al. examined the association between transportation barriers and HIV-related health outcomes by comparing GPS-tracked distance, straight-line distance, and self-reported distance to HIV clinic in Uganda [97]. They found that GPS-tracked and straight-line distance were highly correlated and were associated with missed clinic appointments, while self-reported distance was poorly correlated with such objective measures and was not associated with missed clinic appointments [97].

Seemingly paradoxically, other studies have shown an association between longer distance and favorable health outcomes. A previous analysis of the RFVF cohort showed that cases had 1.25 times the odds of traveling more than 60 minutes to reach the clinic compared to controls, but that they also had 1.29 times the odds of traveling less than 30 minutes as well. While the increased odds of being a case among those with long travel times to McCord may be explained by transportation and structural barriers, the increased odds of being a case among those with short travel times may be explained by stigma related to HIV disclosure [16]. In a study of predictors of successful early infant diagnosis of HIV in a rural district of Mozambique, mothers who lived more than 10 kilometers away from the hospital had approximately 2 times the odds of follow-up for early infant diagnosis compared to mothers who lived less than 10 kilometers away, after controlling for household size, maternal income, maternal literacy, maternal relationship status, and maternal ART status [98]. In Nigeria, Anude et. al. followed 2,585 first time users of ART from three representative government hospital, in order to increase generalizability. A randomly selected 628 of those who survived after 12 months underwent immune-virologic analyses and virologic failure (defined as > 400 copies/mL) was determined. However, after controlling for study site and other potential confounders, it was found that those who lived 51-100 kilometers from their clinic had a statistically significant smaller odds of virologic failure compared to those who lived less than 50 kilometers [99].

In a 48-week-long randomized controlled trial of 499 HIV-infected adults in Nigeria, Taiwo et. al. found that after adjusting for treatment group, gender, age, and HIV disclosure status, living near the clinic was significantly associated with better HIV-related outcomes. For instance, compared to participants who lived greater than 100 kilometers from the clinic, those who lived less than 20 kilometers were more likely to be at least 95% adherent at week 24 (adjusted OR=2.31, $p<0.01$), at least 95% adherent at week 48 (adjusted OR=2.35, $p<0.01$), have undetectable viral load at week 24 (adjusted OR=1.85, $p<0.01$), and have undetectable viral load at week 48 (adjusted OR=1.64, $p<0.05$) [100].

Socioeconomic risk factors: Education, Income, and Employment

While the term socioeconomic status (SES) is used rather frequently as a risk factor for health outcomes, the exact implications of what SES is measuring may differ between studies. SES is "a multidimensional construct" whose measures used to describe SES may emphasize different aspects of the construct [101]. Conceptually, socioeconomic status refers to the natural (e.g. land, water), physical (e.g. roads), financial (e.g. income), human (e.g. education), and social (e.g. networks, family) forms of assets individuals can access to create livelihoods [102]. Thus, in its most simplistic and often used conceptualization, measure of SES is based on individual-level income, employment, and education status. Used as a measure of social stratification, Galobardes et. al. describe the theoretical basis for these three indicators of SES as follows [103, 104].

1. Education: Education aims to capture the knowledge-related assets of a person. As education is most often completed, if completed, by young adulthood, and is strongly influenced by parental characteristics, education can be viewed as capturing early life SES.

2. Income: Income aims to capture the financial- and material-related assets of a person.

3. Employment: Employment aims to capture an individual's social standing in society, which closely relate to both income and intellect [103, 104].

With regards to HIV, these aspects of SES are hypothesized to influence HIV virologic failure through adherence to ART in a multitude of ways; high levels of education provide the "basis for a stable future" for many, setting the foundation for better jobs, greater economic security, and greater autonomy [103, 105]. Such characteristics may affect one's decision-making process regarding ART, prioritizations of ART adherence, reminders to take medications, or knowledge to access and understand disease and treatment [103]. These relationships are closely linked to income and financial capital, which may impact ability to pay for medications and transportation to clinic in the face of other competing, economic priorities, such as food and shelter [102, 106]. One may assume that individuals who are unemployed would also be at greater risk of reduced ART adherence, through similar mechanisms described above. Unemployed individuals may be more likely to have unstable living conditions, which could result in reduced ability to refill medications regularly, obtain transportation, or competing financial priorities [107].

However, the literature shows that the relationships between the components of SES and adherence to ART are not as clear. Several reviews have concluded that while there appears to be a positive trend between increased SES (defined in terms of income, employment, and education) and adherence to ART, the data remain inconclusive. In one systematic review of that reviewed 62 articles in depth for socioeconomic factors that impact adherence to HIV therapy in low- and middle-income countries, a significantly positive association was found between increased adherence and greater income (41.7% of the studies), higher level of education (20.4% of the studies), and employment status (11.1% of the studies) [108]. Although most significant findings referred to such positive associations, one study for income, four for education, and two for employment found an inverse association with ART adherence [108]. A second systematic review found that the associations between income and adherence, and education and adherence were found to be statistically significant in less than a half and less than a third of studies examined, respectively [103]. A third systematic review examining concepts related to SES, such as financial, social, and human capital, in low- and middle-income countries similarly obtained inconsistent findings across studies [102]. However, financial capital was the one key factor found to be significantly associated with adherence. This supports the findings from other studies which have indicated cost of treatment as a barrier for adherence [109]. For instance, a meta-analysis of ART programs in resource-poor settings found that patients who did not have to pay for treatment had a greater probability of optimal ART adherence and achieving virologic suppression compared to situations when patients had to pay for treatment [110]. A study assessing risk factors for medication adherence for the first month following ART initiation in KwaZulu-Natal, South Africa considered interaction effects in their analysis. It was found that the effect of the patient's contribution to household income on ART adherence differed whether the patient at the study's urban versus rural treatment sites, such that those who were not the source of household income in the urban treatment site had over 4 times the odds of adhering to ART compared to their rural counterparts [111].

While increased employment and income may intuitively be presumed to be associated with optimal ART adherence, there are various explanations to justify why they may actually be associated with poorer ART adherence. For example, employed persons often lack time within their schedules to attend clinic appointments and may be more at risk of experiencing discrimination and stigma from coworkers, which can compromise adherence [112]. Similarly, income may provide a distraction from optimal ART adherence through increased recreation and travel. Other explanations are that in certain health care systems, wealthier individuals who are typically insured may have greater out of pocket expenses and run the risk of debt and having to discontinue treatment, compared to poorer individuals who may be more thoroughly covered through public programs, such as that of the Ryan White HIV/AIDs program in the United States [113]. Lastly, some studies have reported lower adherence free ART programs compared to self-pay programs [114-116]. For example, an Ethiopian study found that people were more concerned about their health when they paid for their own treatment [116].

Low level of education has not been consistently associated with poorer adherence to ART [102, 117-119]. For example, a longitudinal study in Brazil found that those with less than 8 years of education had 1.83 times the risk of non-adherence to ART (95% CI: 1.24, 2.69) in a univariate analysis and 1.71 times the risk of non-adherence to ART (95% CI: 1.14, 2.56) in a multivariate analysis after controlling for demographic, risky behavior, clinical, and psychiatric factors [120]. Another study showed that of the 263 interviewed AIDS patients interviewed in a teaching hospital in northern Nigeria, participants with formal education were nearly 4 times more likely to adhere to ART (OR = 3.97, 95% CI: 1.75, 9.24). Among the most common reasons cited for non-adherence included lack of availability of drugs (40.6%), forgetfulness (23.9%), and lack of funds to cover costs (15.8%) [121].

Whereas some studies have found significant associations between lower education and poorer adherence to ART, other studies have indicated that higher education is associated with poorer adherence. In examining predictors of ART adherence among HIV positive patients in Botswana, Weiser et. al. found that patients with incomplete secondary education had nearly 4 times the odds of adhering to ART compared to patients with higher education [109]. A second study among HIV-1 infected adults attending three urban clinics in Cote d'Ivoire found that participants with at least secondary education had almost 2 times the odds of self-reported incomplete adherence to ART [122]. According to a cross-section study conducted in southeast Nigeria, after controlling for sex, age, marital status, employment status, household income, and distance from home to clinic, participants with higher education remained significantly associated with ART non-adherence [123]. A qualitative study in KwaZulu-Natal, South Africa interestingly found that interviewed providers perceived that patients with lower education would have a poor ability to maintain optimal ART adherence, a view with which interviewed patients did not agree [117]. While more highly educated patients may be, “better equipped to plan, organize, and integrate new realities into their daily lives,” which can lead to greater adherence, others hypothesize that higher education patients may be “too busy with their professional activities to take their pills regularly” or may be more aware and weary of side effects for the lifelong regimen [74, 102, 123, 124]. However, it is possible that education functions as a surrogate for employment and income, and therefore the inconsistency in findings regarding education and adherence are in fact due to the relationships of employment, income, and ART adherence.

The literature presents less but still inconsistent findings regarding the relationship between employment and income, and adherence to ART. In several studies, the inability to afford medication and/or the costs of transportation to clinic was among the more frequently reported reason for ART non-adherence, especially in the presence of competing economic priorities such as feeding the family[18, 63, 102, 123, 125, 126]. One cross-sectional study in Ethiopia assessed adherence rates and determinants of adherence among HIV infected individuals, using both qualitative and quantitative methods. It was found that even adjusting for several demographic, behavioral, and clinical factors, unemployment was statistically significantly associated with non-adherence to ART ($OR = 0.01$, $p = 0.007$) [107]. In contrast, other studies did not show an association between employment or greater income and ART adherence [68, 71, 102, 123]. Furthermore, 24 out of the 27 studies examined in a systematic review by Peltzer et. al’s systematic review found no statistically significant association between employment status and adherence to ART [108].

Neighborhoods and Health

Characteristics of a neighborhood's physical and social environment have repeatedly shown to be associated with a wide range of outcomes, ranging from birth weight, chronic disease, mental health, and infectious disease, including HIV[127-138]. However, there is a growing interest in the field of social epidemiology to determine the extent of effects on health outcomes attributed to neighborhood-level characteristics. Within the field of social epidemiology, individuals are viewed as entities within a larger community context, such that characteristics of an individual's neighborhood may impact the individual health outcomes directly or indirectly through individual-level risk factors [139, 140]. Such research questions thus require a differentiation between two distinct group-level factors; one notion describes that an observed neighborhood effect is due to the characteristics of the individuals that happen to make up that neighborhood that exhibits an effect, termed "compositional effects"; the other notion is that true effects exist between a neighborhood's characteristics and a health outcome, regardless of the characteristics of the individuals that make up that neighborhood, termed "contextual effects" [141]. It is possible for health outcomes to be explained by a combination of both such effects, or for interactions to exist between factors in the two groups [142]. Nevertheless, in practice it is typically difficult to distinguish between the two when reliant on traditional logistic regression techniques [142, 143].

In order to distinguish between compositional and contextual neighborhood effects, multilevel regression analysis has become an increasingly popular method in the field of social epidemiology. Multilevel regression modeling allows for the possibility to analyze what proportion of the variation in health outcomes is due to individual-level risk factors and what proportion is due to being part of a particular community [142, 144]. Thus, if healthy individuals correlate to a similar environment, typical multivariate logistic regression will underestimate the standard errors for such neighborhood contextual effects and produced biased results [145]. A systematic review of multilevel regression analyses of various health outcomes contributes to the growing amount of evidence for neighborhood effects on individual health [145].

In examining neighborhood effects on health, neighborhoods can be conceptualized in terms of their physical environments and their social environments, both of which impact HIV-related behaviors [146]. Whereas the physical environment encapsulates the physical and geographical attributes of a community and their effects on health, such as road networks, city planning infrastructure, number and location of health clinics, the social environment describes neighborhoods in terms of social processes, relationships between individuals and groups, behavior, and culture.

These risk factors interact at multiple levels in complex ways to contribute to virologic failure. Individual health is affected by both individual-level (i.e. psychological and socioeconomic) factors and structural-level factors (i.e. economic, institutional, political, and cultural) factors of the individual's environment [146]. This is particularly true for resource-limited settings, where structural factors may play a larger role on impacting individual health [147]. In the context of the HIV epidemic in South Africa, ART adherence and other health behaviors that influences virologic failure has traditionally been characterized as a purely independent act [146]. However, in reality, studies have shown that HIV is closely associated with structural and social aspects of the environment. Thus, a perspective on HIV treatment outcomes that incorporates the influence of poverty and geographic region in explaining the observed patterns of HIV treatment outcomes is vital [148]. Although ultimately optimal adherence is a necessary requisite factor for virologic suppression, there are many upstream risk factors that can predict virologic outcomes (suppression or failure).

Neighborhood-Level Socioeconomic Status

Studies that examine the role of socioeconomic status on health outcomes typically examine the association between individual-level socioeconomic status and individual-level health outcomes. In the field of social epidemiology there has been an increasing interest in the effect of neighborhood-level socioeconomic status on health outcomes above and beyond that of individual-level SES [141].

In parallel to individual-level SES, measures of neighborhood-level SES adapt area-level indicators of education, employment, and income. If there is not a significant association between neighborhood-level SES and individual-level health outcomes after adjusting for individual-level SES, this suggests that the effect of the neighborhood on health is compositional (i.e. attributed to the distribution of individuals and their socioeconomic status within neighborhoods). If, however, significant associations exist between neighborhood SES and health outcomes, after adjusting for individual-level SES, this is evidence that there is a contextual effect of neighborhood on health outcome above and beyond that of individual SES (i.e. neighborhood SES is greater than the sum of individual SES) [141]. Previous studies have examined the role of neighborhood SES on health outcomes, ranging from depression, chronic disease, respiratory function, and smoking for example [139, 149]. However, the number of studies on the neighborhood effects controlling for individual-level effects on HIV treatment outcomes is limited.

Several studies have incorporated population-level factors in understanding individual-level risk of HIV infection. One study utilized both individual and community-level variables for socioeconomic status (defined by income, employment, and education status) in a multivariable logistic regression model to examine the effects of these variables on HIV prevalence among antenatal clinic attendees in South African districts. Their findings showed that both individual and community-level factors exhibited ‘non-linear’ effects on HIV risk. For instance, antenatal clinics in “middle income” districts (defined as annual average income between R15,000 and

R30,000) held the lowest odds of HIV infection, while the odds of HIV infection were greater in both wealthier and poorer districts. Interaction between individual-level factors and community-level factors was present among the domains used to define SES in Kirk's study. This suggests that the effect of an individual's income/employment profile on HIV infection varies depending on the income/employment profile of the community in which the individual lives [150, 151]. Another study conducted in rural Tanzania also found strong associations between select community-level characteristics and HIV incidence. After controlling for individual sex, age, and marital status, living in subvillages of greater socioeconomic activity was associated with greater risk of HIV infection (RR = 2.07, p = 0.1). Similar trends were also observed for more urban subvillages and those with greater mobility of its population [152]. A more recent study conducted in Zambia analyzed the effect of both neighborhood and individual factors on HIV infection among young women. The study created a composite neighborhood-level SES score, based upon categorized rankings of education, occupation and employment statuses, and electricity and water availability, in order to identify risk factor differences between tertiles of neighborhood-level SES scores. After adjusting for individual-level variables, young women coming from "Medium-SES" and "Low-SES" neighborhoods had 2.4 (95% CI: 1.4 – 4.3) and 2.3 (95% CI: 1.3 – 4.2) times the odds of having HIV infection compared to those coming from "High-SES" neighborhoods, respectively [153].

Of the few studies that have incorporated epidemiologic methodology to examine both neighborhood and individual factors for the field of HIV/AIDS, even fewer have looked at HIV treatment outcomes rather than HIV infection. Shacham et. al. conducted a study in the St. Louis, Missouri metropolitan region in order to assess if neighborhood conditions, including percent in poverty, racial composition, and unemployment rates, were associated with HIV management outcomes. In both univariate and multivariate logistic regression models that controlled for several individual level variables, no significant relationship between neighborhood conditions and HIV viral loads existed [154]. Joy et. al. utilized neighborhood level socioeconomic factors from the 2001 Canadian Census database in order to link area variables to patient variables to identify risk factors for HIV-related deaths and for late access to ART. Using multivariate logistic regression analysis, it was found that patients who accessed HIV treatment late tended to live in neighborhoods characterized by high levels of unemployment, after controlling for age, previous AIDS-defining illness, and baseline viral load (aOR = 1.41; 95% CI: 1.14, 1.74). However, since the multivariate model did not control for individual level socioeconomic status, the degree to which this neighborhood is contextual or simply a result of being composed of clusters of unemployed individuals could not be determined [155].

Role of Spatial Analysis: HIV in South Africa

Spatial distribution of health outcomes can be observed from neighborhoods within a local community to regions across countries and the scales in between [156]. A spatial pattern can also be observed for a wide range of health outcomes, including both communicable and non-communicable diseases [156]. The spatial distribution of disease is often linked to the distribution of factors in the social and physical environment [157]. Thus, a more holistic approach to the examination and meaningful interpretations of the associations between individual-level risk factors, neighborhood-level risk factors, and HIV virologic failure is to incorporate visualizations of outcome distribution.

In order to examine spatial distributions of disease, Geographic Information Systems (GIS) technologies are often utilized. ArcGIS is a GIS mapping tool that that allows the user to manage, analyze, link, model, and visualize spatially-referenced data gathered from different sources [158]. GIS programs have historically been underutilized in the field of public health [159]. However, with advances in the availability of spatially referenced data and technologies to conduct spatial analyses, there has been an increase in the use of such methods for epidemiologic studies [160]. Lawson et. al. summarized the primary functions GIS for epidemiology as 1) describe the spatial distribution of disease incidence to generate etiologic hypotheses and 2) to identify and display areas of high and low disease risk to allow for targeted interventions and resource allocation [161]. Maps can be a particularly user-friendly display of health data, facilitating a better understanding of health problems for community members, policy makers, and other stakeholders. Nevertheless, the importance of identifying spatial distributions of disease is not only to identify high-risk areas for targeted interventions, but also to determine if spatial location is a surrogate for otherwise unobserved or under-emphasized risk factors of disease [162]. Such arguments can similarly be applied to spatial analyses of HIV treatment outcomes and virologic failure in South Africa. Descriptive spatial analyses methods are thus particularly useful in highlighting the spatial distribution of those with and without a health outcome, such as virologic failure.

GIS technologies and spatial analyses methods have become increasingly popular in describing the HIV epidemic in South Africa. Research groups have used such methods to identify the spatial distribution of HIV infection across provinces [163, 164], districts [165], and local communities[162, 166-168], some have calculated significant clustering of HIV infection [162, 167], and HIV-related mortality [160]; others have used such methods to estimate average travel distance and times to nearest clinics [169, 170], and develop spatial logistic regression models linking individual- and area-level data [165]. For example, Kleinschmidt et. al. linked continuous HIV prevalence maps for 15-24 year olds in South Africa to socioeconomic data extracted from the 2001 census. Significant univariate associations were found between HIV infection and proportion of 20-64 year-old persons unemployed ($p = 0.032$ females, $p = 0.062$ males) and the proportion of black Africans ($p < 0.0001$ females, $p = 0.028$ males). However, once entered into a multivariate model, only the proportion of black Africans and HIV infection remained statistically significant. This result not only shows the correlation between race and such socioeconomic factors, but the fact the proportion of black Africans and HIV infection *remained* significant after adjusting for socioeconomic factors is likely a result of the historical differences in the HIV epidemic between different race groups in South Africa. Thus, spatial methods have greatly contributed to the growing knowledge of the South African-specific HIV epidemic [165]

Causal Analyses

Since the 1990s, the tools of causal inference have been increasingly applied in epidemiologic research [171]. An essential understanding in using epidemiology to answer causal questions about the relationships between exposures and outcomes is that correlation/association does not imply causation. For instance, if a statistical association is observed between two variables, X and Y, this could indicate one or more of the following relationships: (1) X causes Y, (2) Y causes X, (3) X and Y share a common cause, (4) random statistical fluctuation, or (5) a spurious statistical association was induced by conditioning on a common effect of X and Y [172]. Nevertheless, statistical associations do provide information about causal relationships and such techniques form the basis of many epidemiologic methods [172]. Thus, one major drawback of typical statistical models is that they may embody assumptions that are not made explicit [171]. For instance, "when a statistical association is reported in an epidemiology article, it is generally with the hope (sometimes unstated) of… giving insight into a causal relation" [172]. However, the tools of causal inference, such as directed acyclic graphs (DAGS), can assist in the explicit depiction of assumptions made when creating causal epidemiologic models.

DAGs are simple, flexible diagrams that informally show one's hypotheses and assumptions about the causal relationships between variables. While they are often used after an epidemiologic analysis is conducted in order to hypothesize mediating mechanisms related an exposure and outcome, DAGs are also useful *before* an epidemiologic analysis conducted in order to identify whether conditioning on certain covariates may control for confounding or rather induce a spurious association. They are particularly useful in visualizing the relationship between exposure, outcome, and covariates for understanding of confounding and the potential impact of controlling for certain variables. Greenland et. al. and Hernan et. al. are among those who developed the rules and assumptions inherent to this framework , which has since been utilized by many in understanding particularly social epidemiologic problems [171-173]. Glymour et. al. summarize the assumptions made for causal DAGS as follows:

> (a) (The Causal Markov Assumption): Any variable X is independent of any other variable Y conditional on the direct causes of X, unless Y is an effect of X.
>
> (b) Faithfulness: Positive and negative causal effects never perfectly offset each other, such that if X affects Y from two pathways, one negative and one positive, there will be either a positive or negative association.
>
> (c) Negligible randomness: Statistical associations or lack thereof is not attributed to random variation/too small of sample size.

The most commonly used criteria for identifying confounders are described as follows:

> (a) A confounder must be associated with the exposure under study in the source population.
>
> (b) A confounder must be a risk factor for the outcome, though it does not necessarily need to cause the outcome.
>
> (c) The confounder must not be affected by the exposure or the outcome [172].

These associations are identified statistically, and most often statistical and causal criteria for confounding overlap substantially. However, when conclusions by statistical and causal criteria differ, it is the statistical conclusions that are likely incorrect. Collider bias, which occurs when unnecessarily controlling for a covariate that is not a confounder, can lead to a spurious association between variables when none exists. This example demonstrates the utility of DAGs in determining which covariates to control for in an epidemiologic model [171, 172].

Thus, while DAGs are often presented only after an epidemiologic analysis is conducted, a critical examination of DAGs prior to conducting such an analysis may prove to be useful in understanding whether conditioning on certain variables would control for confounding or instead induce spurious associations by opening confounding or biasing paths.

Study Site and Geographic Considerations

As a result of the prevalence of adverse consequences of virologic failure, the World Health Organization (WHO) has developed an HIV drug resistance prevention and assessment strategy, which includes identifying and monitoring system-level early warning indicators (EWIs). These EWIs are used to identify programs and areas at high risk of HIV drug resistance and include: “retention on first-line ART, on-time drug pickup at pharmacy and clinic appointment keeping, and viral load (VL) suppression 12 months after ART initiation” [26, 174]. While EWIs have typically been used to identify program-level predictors of virologic failure, individual-level factors that can be used by clinicians are just as important [16, 26]. The Risk Factors for Virologic Failure (RFVF) study was initiated to develop a comprehensive assessment of psychosocial, structural, and clinical factors for prediction of virologic failure in KwaZulu-Natal, South Africa [26]. Understanding the influence of recent South African history assists in contextualizing the HIV epidemic in KwaZulu-Natal, particularly in terms of identifying root causes for the characteristic spatial distribution of virologic failure within the study site of the eThekwini district [148].

Durban

McCord Hospital is located in Durban, the largest city in the province of KwaZulu-Natal. Durban is among the most populated cities in South Africa, with around 600,000 in the city center and nearly 3.5 million in the entire Durban metropolitan area. This region is culturally diverse, where Black Africans, Indians, Whites, and Coloureds co-inhabit with most speaking English and/or Zulu [175]. Durban's complex history of colonization and racial segregation provide context to the cultural diversity, social conditions, and geospatial distribution of HIV seen in the region today.

The increasingly segregationist policies implemented leading up to and during the apartheid era greatly impacted the residents of KwaZulu-Natal. Beginning in colonial times, non-whites in South Africa were subject to increasingly more discriminatory legislation, which limited their employment opportunities and housing opportunities. A series of increasingly discriminatory legislation was implemented through the 1900s. While residential segregation existed in South Africa from colonial times, it was not until the Group Areas Act and other similar laws were enacted under the apartheid government that residential segregation along racial lines was controlled and enforced [176]. Forced removals led to the establishment of many informal settlements by black Africans, which continue to exist today.

Under the apartheid government, a system of migrant labor was established in order to maintain a steady flow of cheap black South African labor from rural regions into more urban areas. Apartheid laws prohibited black South Africans from settling permanently in the urban 'white only' regions, thus initiating circular migration patterns where these black workers (primarily men) would move between living in the city in hostels and their rural homes. This movement led to the mixing of urban and rural sexual networks and assisted in the transmission of HIV [177].

Despite the shared history of segregationist policies, residents of different townships were impacted in different ways. As the transmission of and management of HIV is likely related to access to healthcare and socioeconomic status, of particular importance to understanding the spatial distribution of HIV within the Durban healthcare catchment area are the histories of the following townships: Cato Manor, INK, Umlazi, and Chatsworth.

Cato Manor

Cato Manor is a Durban neighborhood located 5 kilometers west of Durban city center. The area was named after Durban's first mayor, George Cato, and given to him in 1865 as recognition as Durban's first mayor. Cato subdivided his land (later referred to as Cato Manor Farm) into smaller-sized plots of land, sold them to prominent White and Indian landowners, who in turn often leased them out to Indian market gardeners and other former indentured Indians. It was such that by the early 1930s a culturally-rich Indian community had formed, where most of the land of Cato Manor Farm was owned by a growing middle class of Indians. As the main source of the city's fruits and vegetables, Cato Manor Farm become crucial to Durban's economy. During this period of time where urban residence restrictions within Durban city center often targeted Indians, Cato Manor became somewhat of a "safe haven" outside of the city boundaries [178]. However, while the municipality developed housing in Cato Manor for Indians, they refused to provide adequate urban infrastructure. Continued legislation restricting land ownership and commercial activity for Indians and Africans in Durban city center in the early 1940s influenced a large influx of African male workers into Cato Manor. Many of them either occupied land informally or leased small plots from landowners ("shacklords") to build their own shacks. For many, illegal beer brewing was their only source of income [178]. Neglected by the municipality, the area eventually became underserviced, overcrowded, and susceptible to poor health conditions [179].

Through the 1930s and into the 1950s, increasingly discriminatory legislation was passed [180]. The Slums Act passed in 1934 assisted slum clearance of Durban city central, which resulted in confiscation of Indian property; the Ghetto Act passed in 1946 enabled the municipality to remove homes under the pretext of improving health conditions [180]. The political climate of Cato Manor Farm changed during the 1940s as tensions grew between cohabiting Africans and Indians and the Durban municipality, led by the Durban City Council which was intent on developing plans to “both control and restrict African and Indian urban residence and economic activity and re-assert municipal authority” [178]. Within Cato Manor Farm sprung up the densely-populated African “shacklands” of Mkhumbane and Wiggins. Social movements amongst both Indian and African communities grew, demanding for equal urban citizenship, adequate amenities, and the right to trade commercially. Despite similar demands by both communities, these social movements began to take on a “racist dimension” [178]. Racial tension grew in the 1940s between African tenants and Indian shacklords, between African shackshop traders and licensed Indian shop owners, between African and Indian shacklords, such that in 1949 violent anti-Indian race riots broke out [181]. Many residents of these African shacklands seized Mkhumbane, proclaiming Mkhumbane “liberated from outsiders” [178]. However, such events consequently turned African shack residents against both Indian communities and the Durban City Council [178]. The race riots accomplished little, in terms of increased rights of urban citizenship. While political leaders amongst the Indian and African communities met to start a campaign against discriminatory legislation, the more extreme demands of the Mkhumbane shack residents which would take away land from Indian landowners could not be met. Instead, a series of forced relocations along racial lines took motion.

The history of the forced evictions of Indians and Africans from Cato Manor greatly influenced the current the spatial distribution of ethnic groups and socioeconomic factors across eThekwini. In 1954 the Durban city municipality established the Cato Manor Emergency Camp, which relocated African tenants while the municipality took over the Mkhumbane area to dismantle the shacklord system and build standardized shack dwellings [178]. However the provisions the government provided in the Emergency Camp were insufficient for its population and health conditions soon deteriorated. Also in 1954 the Group Areas Act was implemented, which enforce racially segregated suburbs in the country (e.g. White, Bantu/African, Coloured, and Asian suburbs) [179]. The Act would consequently rezone Cato Manor as "White only" and would forcibly evict Africans and Indians from Cato Manor to re-settle them into racially segregated townships; Africans were relocated to KwaMashu in the north and Umlazi to the south of Durban city center and Indians to Phoenix in the north and Chatsworth in the south as a buffer zone between Durban city center and KwaMashu and and Umlazi, respectively [181]. Dispossessed landowners were paid insufficient compensation to relocate and many forcibly exchanged full land ownership rights for "weak tenancy rights" in the townships [182]. For many, relocation also meant exorbitantly high rent prices and increased distance with inconvenient transportation routes to their places of employment [179].

The relocations were met with substantial resistance. Reports have suggested that while 80,000 Africans were officially relocated, around half of those never made it, either having returned to rural areas or found residence elsewhere [182]. A wave of violence spread during this time, namely influenced by the group of illegal beer brewers from Cato Manor whose forced relocation and demolition of their homes also destroyed their single source of income [181]. Cato Manor was unable to fully develop into a "White only" zone due to substantial resistance against the Group Areas Act that "cut across race and class boundaries" [182]. Cato Manor was never completely cleared of Indian residents and in 1980 was reopened for Indian land ownership [178, 181]. The Cato Manor Development Association (CMDA) was established to provide much needed infrastructure for the area. Today, eThekwini municipality manages the development of the area.

Inanda, Ntuzuma, and KwaMashu (INK)

The region termed as “INK” includes the townships of Inanda, Ntuzuma, and KwaMashu, which account for 50%, 18%, and 32% of INK’s population respectively [183]. The vast majority of residents of INK are black Africans (99%) and speak Zulu as their first language (95%) [183]. A primarily urban residential area, INK is situated approximately 20km north-west of Durban city center, with a high density of housing [184]. INK is located at the periphery of Durban, where it is isolated from the city center and other populated township ‘nodes’ by the Umgeni River Valley, hilly terrain, and a vast ‘buffer’ zone of uninhabited green space as a result of city planning during apartheid [183]. The three towns that make up INK are characterized by similarly high levels of poor socioeconomic status. For instance, over a third of households in INK earn between R800 (rand) and R3200 (rand) per month, indicating a poor quality of life [185]. The high levels of poverty in the region are likely a reflection of the reduced employment opportunities for the INK population, where around 40% of working-age people are unemployed and 34% have never attended school [184]. Despite that the majority of housing in INK is formal, around a quarter of households do not have electricity and around a third do not have piped water [183]. Furthermore, the geospatial distribution of formal housing is not evenly spread; 90% of housing is formal in KwaMashu compared to around 50% of housing in Inanda [183]. The impoverished statuses of INK, and many other townships in Durban, are lasting consequences of how these townships were initially developed and affected by apartheid policy.

Inanda

Of the three townships that make up INK, Inanda is the oldest. It was initially established by Boers in the 1830s, when the region was under control of the Boer Republic. Between the 1840s and 1920s, many ex-indentured Indian farmers and wealthy Christians from the Inanda mission were able to buy land in the area and make a decent living from crops, such as sugar cane. Indian and African communities in the area coexisted peacefully in the area during this time. However, in the 1930s, as a result of the increasingly discriminatory legislation being passed, all of the private landholding in Inanda was designated as a "Black African reserve," destabilizing many residents' sources of income. After Cato Manor was destroyed and Africans were forcibly moved to townships such as KwaMashu, those who couldn't find jobs moved further out to places like Inanda. Inanda saw an influx of impoverished people unable to find work, forcibly removed from their homes, and/or coming from drought stricken rural areas. Many of those who maintained land in Inanda became 'shack farmers,' renting out plots of land for informal shacks to be built. By the 1980s Inanda had evolved from a quiet shantytown, to an overcrowded impoverished region characterized by high levels of unemployment, poverty, and violence [186, 187]. Today Inanda is one of the poorest areas of the eThekwini municipality, where 43.5% of households live under the national poverty line and 31.2% of persons are unemployed [188-190].

KwaMashu

Following chronologically, KwaMashu was the second town of INK to develop. The name "KwaMashu" roughly translated into Zulu means, "the place of Marshall," in reference to a Sir Marshall Campbell (1848-1917), who owned a sugar cane plantation where KwaMashu resides today. The KwaMashu township was created as a place to forcibly resettle former residents of Cato Manor after it was cleared. KwaMashu was purposefully designed with buffer zones between African and Indian neighborhoods with no connecting roads between them and with very limited input allowed from Cato Manor residents. KwaMashu began to be constructed in 1957, and starting in 1958 African people were moved in by the thousands. By 1962, around 40,000 people occupied KwaMashu, many removed from Cato Manor but also other locations. In addition to the chaos the forced re-settlement of many Africans in KwaMashu caused, many new residents often now faced longer travel times and overall higher travel costs to their places of employment [191]. According to the 2011 South African census, 30% of persons are unemployed and around 38% of households live in poverty, both measures which are higher than the eThekwini municipality median. Over half of KwaMashu's 20 + year old residents have less than a complete secondary education [188-190].

Ntuzuma

Established in the 1970s, Ntuzuma is the newest of the three townships that comprise INK. It was built by the Durban city government in incrementally different sections overtime. Such township development has likely influenced the characteristics of each section, varying in housing arrangements and levels of services provided. Nevertheless, Ntuzuma is largely occupied by informal housing (40% of households are informal) [183, 192]. Furthermore, 26.6% of 15+ year olds are unemployed, 58.8% of 20+ year olds have less than a complete secondary education, and 32.1% of households live on R9,600 per year, approximately corresponding to the R7,440 upper national poverty line [188-190, 193].

INK

The INK Economic Strategy Document of 2006 attributes much of the poor economic landscape of the INK region to the situation of South Africa's dual economy: the first economy, which is competitive and well developed, and the second economy, which was "exacerbated by apartheid planning" and is marginalized and underdeveloped. INK's economy falls into the second category, where there is little revenue growth occurring within INK. The development of business initiatives to stimulate growth within INK is hindered by the low buying power of its residents, inadequate infrastructure, and lack of financial support services. As a consequence of the marginalization experienced during apartheid, worsened by the reinforcing low economic activity in INK, the area experiences: inadequate water supply, high unemployment, crime, lack of legal ownership over housing which thus cannot be used as an economic asset, and poor access to and maintenance of governmental and municipal services (e.g. hospitals, police stations, parks, public transportation, etc.) [185].

The current state of transportation servicing INK is inadequate to meet the needs of the INK population. About 70% of employed residents work outside of INK. Many of these residents thus rely on walking and/or public transportation to arrive to work, but many areas are not serviced by buses or taxis and have inadequate sidewalks for pedestrians [183, 185]. Those transportation routes that are available typically only link INK to Durban city center, making it difficult for residents to travel within INK itself [183]. For instance, while KwaMashu is well connected to the city center via rail transport, minibus taxi, and buses, travel within the township remains expensive and constrained [184].

In an attempt to address the infrastructure deficiencies in INK and other townships, and improve their integration with other nodes, the national government created the Urban Renewal Program in 2001. By 2009 improvements were made in INK that extended provincial roads to link INK with other township nodes, such as Pinetown and New Germany, and internal roads, such as those that link to KwaMashu and Bridge City [183]. The program has also extended railway routes and built taxi stands at key transportation hubs that already exist within INK, such as in KwaMashu. Furthermore, since 1999, the KwaMashu Town Centre has undergone major infrastructure improvements, including but not limited to: improved road access within KwaMashu, land ‘packages’ serviced by water, electricity, and sewerage access prepared for private-sector development, improved recreational areas, increased security presence, and increased social services (e.g. healthcare clinic) [194].

Umlazi

The Umlazi township is located around 17 km south of Durban city center. The history of the Umlazi area dates back to 1845, when British settlers occupied the Zulu’s land. In accordance with the British empire’s mission of spreading Christianity, the Umlazi region become one of many ‘Mission Reserves’ in the area. However, starting in 1940 plans were being made to convert Umlazi Mission Reserve into a township due to its relative low occupancy at the time and its physical isolation from Durban city center [179, 195]. Thus, following the Group Areas Act in 1954, Umlazi became designated as an African township, primarily for those who were evicted from Cato Manor. Those who moved into Umlazi experienced many of the difficulties as previously described, including increased unaffordable rent prices and decreased accessibility to the city center [179]. The effects of the urban planning policies that created physical and economic isolation in Umlazi during the apartheid era continued to be felt today.

As one of South Africa’s most populated townships with high density housing, Umlazi is home to approximately 550,000 individuals. Umlazi’s problems are typical of many townships, such as deficiencies in proper housing, provision of facilities and services, access to surrounding regions, and economic opportunities within Umlazi [195, 196]. For example, main access to and within Umlazi is dependent on individual major roads running north/south and east/west. However, major linkages to many neighboring townships, such as to Chatsworth, do not exist. Furthermore, while Umlazi does have a town center, it has experienced little economic development. Most residents instead must travel to neighboring areas, such as Isipingo, for many goods and services, further outsourcing potential investment into the community [196].

The reduced economic opportunities and transportation issues in Umlazi have likely contributed to the region's high unemployment and crimes rates. For instance, according to the 2001 Census, 38% of Umlazi's working age population is employed in the formal economy. This is likely attributed to the fact that most people in Umlazi have at most a Grade 10 level of education and thus termed "semi-skilled" or "unskilled" for many occupations. However, there is a portion of the population that engages in informal activities, working as temporary or casual workers that are not accounted for in the census. Thus, while reports suggest that almost a third of the population have no source of income, this statistic may not account for the limited informal activities of work. Nevertheless, Umlazi has experienced little economic development, attributed to the economic and physical isolation established during apartheid. Umlazi is comparable to other townships with its large informal settlements and high crime rates. Such high levels of crime have the potential to further impede business investment into the area [195, 196]. According to 2011 census data, approximately a third of eligible persons are unemployed and a half of adults have less than a complete secondary education. In Umlazi, approximately 36% of households live on R9,600 per year which nearly corresponds to the upper national poverty line of R7,440 per year [188-190, 193].

Chatsworth

Chatsworth was historically an Indian region of Durban. Many of the first Indians came to South African as indentured servants starting in the 1600s. Many of those who completed servitude and remained in South Africa made a living through agriculture as market gardeners or opened stores and hotels. An influx of non-indentured Indians arrived starting in the 1860s to supply the demand for traders. With the success of many Indian traders came increased racial tension between White traders, a group of whom lobbied the government to pass legislation to restrict Indian trader's rights. Many Indian laborers settled in pockets within Durban city center and its outskirts, such as Cato Manor and Phoenix (the settlement founded by Mohandas Gandhi in 1904 [197]. However, housing shortages caused many areas to become overcrowded with slum-like conditions. Discriminatory tension against Indian immigrants grew, with many residents of Durban regarded their arrival as “unwarranted intrusion upon the colonial atmosphere” [180].

Even though informal racial segregation existed at the time, the series of legislation leading to the Group Areas Act negatively impacted the socioeconomic conditions of many Indian communities, in addition to Black Africans. The establishment of Chatsworth as an Indian township is a direct result from the Group Areas Act. Many Indians who were forcibly removed from Cato Manor ended up in Chatsworth. The location of Chatsworth was purposefully chosen to function as a buffer zone between the White residential areas in Durban city center and the Black African township of Umlazi [180, 198]. What the experiences of residents of those and other townships in the Durban area have in common are the lasting effects from apartheid and discriminatory policy on defining the social environment of South Africa and its provinces and districts today. These histories provide contextual justification the spread of neighborhood-level characteristics of SES around the Durban area. The forced removals, the limited employment opportunities, and the complicating and limiting of transportation infrastructure, contextualize and may explain why certain areas have poorer neighborhood-level indicators of health. A person’s place of residence is tied into community-level factors of the social environment. If one believes that the spatial distribution of patients with HIV treatment failure is not randomly distributed, but rather a manifestation of the community-level effects that go above and beyond individual level effects (a contextual effect), in causing HIV treatment failure, then this would identify particular areas of importance of further investigation/identifying high risk areas of treatment failure attributed to neighborhood effects and not solely individual effects.

Study Site

Sinikithemba Clinic (SKT) was an outpatient HIV clinic at McCord Hospital (MCH) in Durban, South Africa, the largest city in the KwaZulu-Natal province. It was established in 1998 to provide outpatient care to HIV-positive patients and their families. In 2004, SKT received external funding from the President's Emergency Plan for AIDS Relief (PEPFAR). The economic support from PEPFAR and the KwaZulu-Natal Department of Health subsidized nearly half of the operational costs of the clinic and allowed Sinikithemba's ART program to expand [199]. However, in 2012 McCord Hospital succumbed to an external financial crisis, namely as a result of withdrawal of 85% of funding from PEPFAR [199]. In recent years, McCord was turned over to the KwaZulu-Natal health department and as of August 2014 was to be converted into a Center of Eye Care Excellence [200].

During its operation, SKT at McCord provided HIV care in an outpatient setting to approximately 6,000 patients per year. Patients paid a fixed clinic fee of $15 USD for clinic services, which covered all medical expenses [16]. In accordance with guidelines set by the South African Department of Health, SKT would monitor HIV-1 viral load and CD4 cell count every 6 months or more frequently if indicated [16, 38]. Additionally, staff would provide adherence counseling prior to ART initiation as well as after any elevated viral load [38].

Taking an ecological approach, where Main Places are considered the unit of analysis, this secondary analysis of the RFVF study data aims to answer the following questions:

1. Is there a population-averaged association between neighborhoods' socioeconomic status and odds of HIV virologic failure even after adjusting for individual-level SES factors?

2. Is there a population-averaged association between neighborhoods' socioeconomic status and odds of HIV virologic failure even after adjusting for individual-level SES factors, when considering men and women separately?

Chapter II: Manuscript

Title/Authors/Abstract

Title: The Association Between Neighborhood-level Poverty and HIV Virologic Failure Differs by Gender in Durban, South Africa: A Multi-level Analysis

Authors: Daniella Coker, BA, Vincent Marconi, MD, Michael Kramer, PhD

Objective

If left inadequately diagnosed or untreated, HIV virologic failure (VF) can lead to acquired drug resistance or early mortality. Gender differences in predictive risk factors for VF, such as individual-level socioeconomic status (SES), have been found. In order to characterize the mechanisms through which SES impacts VF, it is important to also consider the role of neighborhood-level SES.

Methods

This is a secondary analysis of the Risk Factors for Virologic Failure (RFVF) case-control study of HIV positive patients residing in eThekwini and attending McCord Hospital in Durban, South Africa between October 2010 and June 2012, after at least 5 months of their first ART regimen. Cases were those with virologic failure (VL > 1,000 copies/mL) and controls were those without virologic failure (VL ≤ 1,000 copies/mL). Multilevel logistic regression (GEE) models incorporating interaction by gender were used to assess the gender-specific associations between neighborhood-level poverty and VF after controlling for individual-level demographic, clinical, and SES factors.

Results

152 cases and 286 controls representing 52 neighborhoods (Main Places) were included in this analysis. Most patients in the sample were female (64.6%), came from high poverty neighborhoods (60.7%), were employed (72.4%), and had at least some secondary-level education (80.6%). In a GEE model only containing gender, neighborhood-level poverty, and their interaction term (Model 1) the OR for the effect of residence in low versus high poverty neighborhoods for men was 1.42 (95% CI: 0.79, 2.53) and for women was 0.76 (95% CI: 0.48, 1.22). Adjusting for individual-SES and clinical factors (Model 3: OR_{men} = 1.23; 95%CI = 0.63, 2.43 and OR_{women} = 0.75; 95%CI = 0.49, 1.15) provided similar results for both men and women compared to when only CD4 count was adjusted for (Model 4: OR_{men} = 1.28; 95%CI = 0.64, 2.55 and OR_{women} = 0.74; 95%CI = 0.48, 1.16).

Conclusions

After controlling for individual-level socioeconomic (SES) and clinical factors, men living in richer areas and women living in poorer areas had greater tendency for VF, perhaps partly due to gender-specific HIV-related stigma. Future studies should employ mediation analyses to further characterize potential mechanisms through which neighborhood-level SES effects may impact VF differently for men and women.

Introduction

With over 5.6 million people living with HIV, South Africa has more people living with HIV than any other country in the world [1]. The province of KwaZulu-Natal on the eastern coast of the country remains at the epicenter of the HIV epidemic [7]. According to the South African National HIV survey of 2012, the prevalence of HIV among 15-49 year olds has increased from 15.7% in 2002 to 27.9% in 2012, which represents the highest prevalence of any other province in South Africa [4]. HIV prevalence in KwaZulu-Natal can be as high as 40% among women attending antenatal clinics [7]. With the success of antiretroviral therapy (ART), HIV has become a chronic disease that requires lifelong therapy and has allowed many to live longer with HIV. Since 2004, when ART began to be offered free of charge, South Africa has experienced a dramatic increase in ART access. By the end of 2012, 2.3 million people were being initiated on ART and HIV treatment coverage had reached 83% according to WHO 2010 treatment guidelines [19-21]. However, as ART availability and the number of individuals living with HIV continue to increase, the proportion of patients for whom it is difficult to retain in care will likely increase as well, creating additional challenges for timely identification and management of treatment failure [16, 26].

To ensure the success of ART, it is crucial to effectively manage and treat virologic failure (VF) among HIV patients. Virologic failure occurs when an ART regimen is unable to maintain maximum virologic suppression and HIV viral replication rebounds, resulting in a loss of the clinical benefits obtained through ART [28]. Studies have indicated the prevalence of virologic failure (VF) in patients on first-line ART to be around 15%, with estimates from second-line ART to be closer to 40% [33-35]. While the proportion of ART users with VF is relatively low, the numbers of HIV patients affected by VF is a growing problem due to the extent of the HIV epidemic in South Africa and the increasing number of individuals starting ART every year. Continuing a failing HIV treatment regimen on which VF was identified is associated with adverse outcomes, such as acquired drug resistance [33, 34, 38] and death [36].

Acquired drug resistance is of particular concern because it can lead to limited affordable treatment options, spread to newly infected individuals, and result in a potentially greater risk of mortality [28, 39, 43, 45]. Thus, successful monitoring and prevention of VF is key to the improvement of treatment outcomes in the post-HAART era.

Routine HIV viral load monitoring in conjunction with CD4 count is becoming the preferred indicator of treatment failure in most settings [27, 32]. The optimal threshold for defining virologic failure and thus switching ART treatments has yet to be established. Effective identification and treatment of VF can be complicated in resource limited settings, where laboratories may lack the resources to accurately diagnose VF (i.e. CD4 count and plasma HIV RNA concentration) and identify major drug resistance (i.e. drug-resistance profiles) in order to inform second-line ART recommendations [201]. Therefore, risk factors for VF may be of particular importance for improving treatment outcomes in settings where access to these tests is not reliable. Optimal adherence to an ART regimen is a key predictor of HIV health outcomes [47]. Research indicates that consistent high levels of adherence are necessary in order for successful viral suppression [49-53] and prevention of acquired drug resistance [54-57], disease progression [58], and death [59]. Despite the benefits of high adherence, non-adherence to ART in adult populations in South Africa has been estimated to be between 10% and 37%, signifying a need for continued improvement of ART adherence [64-68].

Substantial research has been conducted on risk factors for VF and risk factors for ART adherence, a potentially key precursor to VF. According to the literature, men typically have worse HIV treatment outcomes, including greater loss to follow up, mortality rates, and HIV virologic failure compared to women [33, 76, 77, 79, 202]. Additionally, in many countries gender disparities may lead men and women to have different experiences with and barriers for ART adherence [92, 203]. Therefore it is important to consider risk factors for VF separately for men and for women. Studies have also identified shorter duration of ART treatment as predictive of VF, perhaps due to less time to have established an effective routine for taking medication [60, 87, 88]. Younger age has also been associated with VF, perhaps attributed to peer discrimination and multiple social distractions [84-86].

One set of risk factors of particular importance for low and middle-income countries such as South Africa is that of socioeconomic status (SES), most often defined in terms of individual-level education status, employment status, and income. Yet, the literature shows inconsistent findings for the relationships between SES and ART adherence or VF. For instance, some studies found higher education is associated with either greater adherence [120, 121, 124], or reduced adherence [74, 109, 122, 123]. Less but still inconsistent findings regarding the relationship between employment and income, and adherence to ART are represented in the literature. In several studies, the inability to afford medication and/or the costs of transportation to the clinic was among the more frequently reported reason for ART non-adherence, especially in the presence of competing economic priorities such as feeding the family [18, 63, 102, 109, 123, 125, 126]. In contrast, other studies, including 24 out of 27 studies examined in a systematic review by Peltzer et. al, did not show an association between employment or greater income and ART adherence [68, 71, 102, 106, 123]. While more highly educated patients may be, "better equipped to plan, organize, and integrate new realities into their daily lives," which can lead to greater adherence, others hypothesize that higher education patients may be "too busy with their professional activities to take their pills regularly" or may be more aware and weary of side effects for the lifelong regimen [74, 102, 123, 124]. However, it is possible that education functions as a surrogate for employment and income and therefore the inconsistency in findings regarding education and adherence are in fact due to the relationships of employment, income, and ART adherence.

In the last 20 years, there has been a changing focus from individual-level factors to how "broader social contextual factors" impact health [204, 205]. The increase usage of new methods such as multilevel regression modeling has allowed studies to determine the presence of neighborhood effects, and whether such effects are compositional (i.e. attributed to the distribution of individuals and their characteristics inside neighborhoods) or contextual (i.e. attributed to characteristics of neighborhoods that go beyond the distribution of individuals) [141]. Previous studies have examined the role of neighborhood SES on health outcomes, ranging from depression, chronic disease, respiratory function, and smoking for example [139, 149, 206-208]. The number of studies examining the role of neighborhood SES and HIV treatment outcomes is limited, yet suggestive of neighborhood effects of community-level SES on HIV-related health outcomes [152, 154, 155]. Such findings are not only crucial for better understanding the mechanisms by which SES may contribute to VF, but also for identifying community-level intervention targets for broader public health impact.

A neighborhood-level approach to understanding risk factors for VF in KwaZulu-Natal is of particular interest given the unique sociocultural and historical context of the region. The physical and social environment of the larger Durban area is largely part of the lasting effects of the increasingly discriminatory policies, forced relocation, and further marginalization experienced by Black Africans and Indians during the apartheid era [148, 176, 179, 185]. As a consequence of the marginalization, worsened by reinforcing low economic activity, many townships eventually became underserviced, overcrowded, deficient in proper housing, and susceptible to poor health conditions. Reduced economic opportunities have also left many areas with high unemployment and crime rates [185, 191, 195]. Furthermore, the urban development of these townships left many of them with insufficient public transportation, inadequate sidewalks, and road networks that continue to leave some areas with reduced access [183, 184, 194]. Thus it would be important to consider these socioeconomic, social, and physical characteristics of the Durban area in assessing the impact they may have on ART adherence and virologic failure.

In order to better characterize predictor factors for HIV virologic failure in the KwaZulu-Natal province of South Africa, the Risk Factors for Virologic Failure (RFVF) study [26], examined a range of demographic, clinical, socioeconomic, and psychosocial factors and identified those most statistically significantly associated with VF for a cohort of 458 HIV-positive patients in urban and peri-urban settings around Durban, South Africa [16, 26]. A subsequent analysis from the RFVF study examined gender-specific socioeconomic risk factors for virologic failure and found evidence that significant risk factors for VF differed between men and women [16]. Both of these analyses focused on identifying characteristics of individuals that can be used to define who may be at higher risk for VF, which may be particularly useful in screening procedures by clinicians. However, an analysis that includes consideration of characteristics of neighborhoods, such as neighborhood SES, may provide deeper insight into the systems-level mechanisms by which VF arise within the sociocultural and historical context of Durban.

In this analysis, we examine the impact of the socioeconomic status of neighborhoods that goes above and beyond that of individuals' socioeconomic factors on HIV virologic failure and how this impact may differ for men and for women living with HIV and attending McCord hospital in Durban, South Africa for HIV care. In doing this analysis we hope to shed light on the mechanisms through which VF occurs and investigate what role social processes measured through neighborhood socioeconomic factors play in these mechanisms.

Methods

Study Location

This secondary analysis uses data collected by the Risk Factors for Virologic Failure (RFVF) study. The RFVF study was conducted at Sinikithemba Clinic (SKT), an outpatient HIV clinic at McCord Hospital (MCH) that closed in 2012 [199]. Sinikithemba Clinic was located in Durban, South Africa, the most populous city in the KwaZulu-Natal province. It was established in 1998 to provide outpatient care to HIV-positive patients and their families. In 2004, SKT received external funding from the President's Emergency Plan for AIDS Relief (PEPFAR). The economic support from PEPFAR and the KwaZulu-Natal Department of Health subsidized nearly half of the operational costs of the clinic and allowed Sinikithemba's ART program to expand [199]. However, in 2012 McCord Hospital succumbed to an external financial crisis, namely as a result of withdrawal of 85% of funding from PEPFAR [199]. In recent years, McCord was turned over to the KwaZulu-Natal health department and as of August 2014 was to be converted into a Center of Eye Care Excellence [200].

During its operation, SKT at McCord provided HIV care in an outpatient setting to approximately 6,000 patients per year. Patients paid a fixed clinic fee of $15 USD for clinic services, which covered all medical expenses. In accordance with guidelines set by the South African Department of Health, SKT would monitor HIV-1 viral load and CD4 cell count every 6 months or more frequently if indicated [16, 38]. Additionally, staff would provide adherence counseling prior to ART initiation as well as after any elevated viral load [38].

Study Design

The RFVF study utilized a density-type case-control study design to investigate potential risk factors for HIV virologic failure, as described elsewhere [26]. Enrollment into the RFVF study occurred between October 2010 and June 2012. For inclusion into the RFVF study, participants met the following inclusion criteria: ≥ 18 years of age, HIV positive, on first regimen of ART for ≥ 5 months, and receiving care at MCH [16]. Cases were patients with virologic failure (VF), defined as having a single viral load measurement of > 1,000 copies/mL. Controls were patients without virologic failure (VF), defined as having a single viral load measurement of ≤ 1,000 copies/mL. Cases were identified as meeting the above criteria and having VF within 1 – 2 weeks of a visit to the clinic. As cases were enrolled into the RFVF study, controls were randomly selected patients in the clinic who met the inclusion criteria and agreed to participate.

Two controls were selected for every case enrolled. Controls were not matched on any known predictors of virologic failure [16, 26].

Upon enrollment, study participants completed a survey which collected information in the following domains: demographics, socioeconomic status, HIV medication adherence issues, alternative and traditional medicine use, psychosocial factors, and medical and HIV treatment history. Data for the present analysis were based on questions from the demographics, socioeconomic status, and medical and HIV treatment history domains of this survey, which included questions regarding basic demographic information, education, employment, relationship status, living situation, transportation to clinic, and funding for clinic.

Study data were collected and managed using REDCap electronic data capture tools hosted at Emory University.

Data Sources

<u>ArcGIS Shapefiles</u>

ArcGIS – ArcMap 10.2 was utilized to map individuals' home addresses and to spatially join individual-level data to neighborhood-level data. Boundary shapefiles and metadata were based on data collected by the 2011 South African Census [209] and accessed through Open Africa [210]. Neighborhood was defined at the Main Place level of the 2011 Census, level 4 of hierarchical structures of geographical entities in South Africa (Figure 2).

In order to reduce distance distortions within the study area, all shapefiles were projected to the Universal Transverse Mercator (UTM) Zone 36S projected coordinate system. Address information (street, area, city) was extracted from the RFVF study and geocoded using the Google Geocoding API in R. For those addresses that could not be mapped to a particular GPS coordinate using the Google Geocoding API, they were re-matched to a GPS coordinate according to either: (a) manual re-matching to the correct street using Google Maps and retrieving the street's center as the GPS coordinate, (b) the GPS coordinate of the physical centroid of the appropriate Sub Place or (c) the GPS coordinate of the physical centroid of the appropriate Main Place. Addresses that could not be mapped by either of the aforementioned means were excluded from analysis. In order to link individual-level data to Main Place data, the home address shape file was linked spatially to the 2011 Census Main Place shapefile.

Cases, controls, and McCord Hospital were mapped as point data (Figures 4 and 5). Euclidean distance was calculated in meters from McCord Hospital to each of the mapped data points.

Statistics South Africa 2011 Census

Neighborhood characteristics at the Main Place and Sub Place level for the eThekwini Municipality were obtained from Statistics South Africa's 2011 South African Census. EThekwini Main Place and Sub Place neighborhood data included: household counts by median annual household income category, and individual counts by employment status for individuals 15 years of age and older and education status for individuals 20 years of age and older. For those Main Places where a discrepancy existed between the Main Place naming scheme from the census tabular data and the census GIS shapefiles, Google Maps was used to re-match the neighborhood characteristics data to match the naming scheme of the GIS shapefiles. Those areas that could not be re-matched and those areas outside of the eThekwini municipality were excluded from further analysis.

Neighborhood data were summarized using culturally appropriate summary measures. Neighborhood poverty was summarized as percent of households in each Main Place living under the poverty line. External sources cite R7,400 (Rands) as the upper national poverty line, adjusted for March 2011 inflation rates, below which persons cannot purchase both adequate food and adequate non-food items [193]. In our data the poverty threshold was defined at an annual income of R9,600 (Rands), which was the income bracket created by the census that was closest to the national poverty line. Unemployment status per Main Place was summarized as percent of individuals 15 years of age and older who self-reported as "unemployed" or "discouraged work-seekers" (individuals who had given up trying to find work). Thus, percent unemployed excluded others not economically active such as students, homemakers, and retired individuals. Incomplete education status per Main Place was summarized as percent of individuals 20 years of age and older who had either no schooling or whose last year of schooling was at most some of secondary school, the minimum compulsory requirements in South Africa [211].

Main Place was defined as a neighborhood for the purposes of this analysis. The three Main Place-level variables (percent of households living under the poverty line, percent of people unemployed, and percent of people with low education) were reported as continuous measures. In order to determine appropriate categorization for each variable, changes in odds ratios were assessed when data were divided into different number of groups. For each of the three Main Place-level variables, data were first divided into nine groups and odds ratios were calculated for each of the nine groups. Odds ratios point estimates and 95% confidence intervals were compared across each of the nine groups. Within each Main Place-level variable, all odd ratio 95% confidence intervals exhibited substantial overlap. This process was repeated separately for data divided into six, five, four, three, and two groups. Similarly, all odd ratio 95% confidence intervals within each variable grouping exhibited substantial overlap. Even though data exhibited relative linearity, for simplicity of communication, Main Place-level variables were analyzed as binary variables. The threshold for distinguishing between a "poor" and a "not poor" neighborhood for the 52 Main Places represented in the study utilized the overall eThekwini municipality (203 Main Places) median proportions of neighborhood poverty (28.9%), unemployment (27.3%), and incomplete education (65.4%).

Study participants were plotted as point data overlayed on “low poverty” and “high poverty” polygon shapefiles for the eThekwini municipality (Figure 6).

Risk Factors for Virologic Failure (RFVF)

Individuals were excluded from the analysis if their home residences could not be geocoded, their homes were outside the study area of eThekwini municipality, or if no census data were available for the individuals’ Main Places. Variables identified from the RFVF study for analysis included demographic, socioeconomic, and clinical variables of importance to describing HIV virologic failure. Cut-off points for variable categorizations were informed by contextual research and significant changes in odds ratios. Demographic variables included: gender, age at study enrollment, last grade of education, marital status. Last grade of education was categorized as $\leq 6^{th}$ grade, 7^{th} to 9^{th} grade, and 10^{th} to 12^{th} grade, which correspond to the South African traditional structures of primary school, compulsory grades of secondary school, and non-compulsory grades of secondary school respectively [211]. Marital status was categorized as either “In a relationship” or “Not in a relationship.” Age was categorized into tertiles, as <= 35 years, 35 to <= 46 years, and 46 to <=73 years. Race was excluded from the analysis due to the vast majority of black Africans who made up the study data.

Socioeconomic variables included: income status, employment status, employment type, living arrangement, mode of transportation to clinic, travel time to clinic, distance between home and clinic, source of payment for medication, number of economic dependents, and number of cohabitants. Employment status was defined as either “Employed”, “Unemployed,” and “Other,” defined as students, retired, disabled, and other non-economically active individuals. Free response answers for type of employment were categorized into basic labor, skilled labor, and professional labor based on contextual research, including interviews with ART counselors. Living arrangement was separated as “Own a house,” “Rent,” or “Dependent living,” defined as living with a friend, family member, employer, or other dependent living arrangement. Mode of transportation to clinic was categorized as either “Car”, “Mini-Bus/Bus,” or “Other,” defined as walking or other mode of transportation. Mode of transportation to clinic for “Car” also coincided with “Car ownership”. Travel time to clinic was based on self-reported ranges of travel time to clinic. Distance between home and clinic was measured as straight-line distance in meters using geocoded addresses of houses and McCord clinic in ArcGIS, and was analyzed as a “< 10km” “10-20km” and “> 20km”. Source of payment for medication, as a measure of economic independence, was categorized as “Self-Pay,” “Family Member,” or “Other,” which included employer, grant, sponsor, or other as sources of payment for prescribed ART. Number of economic dependents and number of cohabitants exemplified similar distributions and were both analyzed as 0 to 2, 3 to 5, and greater than 5.

Clinical variables of importance for describing HIV virologic failure included CD4 count at study enrollment and years on ART. CD4 count at study enrollment was categorized according to Centers for Disease Control and Prevention (CDC) CD4 cell count categories used alongside clinical categories for HIV-staging classification [212, 213].

Causal Analysis

Causal analysis for the variables of interest consisted of developing an appropriate directional acyclic graph (DAG) based on relationships described in the literature. Confounding and mediating relationships between neighborhood SES and virologic failure that included study variables of interest were incorporated into the DAG. The relationships described in Figure 1 may either encompass positive relationships, negative relationships, or both.

Statistical Analysis

All data were analyzed using SAS 9.4. Neighborhood-level variables were linked to individual-level variables using ArcMap 10.2. REDCap electronic database was used for storage of all data.

Descriptive statistics for all neighborhood-level exposures (% households under poverty line, % unemployed persons, and % persons with incomplete education), covariates, and the outcome (virologic failure status) were performed. Frequency distributions of each of the covariates for the 438 individuals were compared by case status (cases, or those with virologic failure, defined as viral load > 1,000 copies/mL versus controls, or those without virologic failure, defined as viral load < 1,000 copies/mL), and by exposure status for each of the three exposures. Statistically significant frequency distribution differences were measured using Chi-square tests.

Correlations between the three neighborhood-level SES variables were assessed to determine whether separate analyses were deemed necessary. Once normality was confirmed for each of the three continuous variables of neighborhood poverty, unemployment, and education, Pearson correlation coefficients were calculated for each of the three paired combinations of variables. The following thresholds were used to determine the strengths of each correlation: R = |.01| to |.19| = No or negligible relationship, |.20| to |.29| = Weak relationship, |.30| to |.39| = Moderate relationship, |.40| to |.69| = Strong relationship, |.70| to |1| = Very Strong relationship [214]. If all three neighborhood SES variables exhibited "Very Strong Relationships," then the scope of the analysis would only consist of one of these variables.

Univariate analyses of each covariate for case status and neighborhood-level poverty were performed, one assuming statistical independence of individuals using normal logistic regression and one assuming statistical dependence of individuals using generalized estimating equation (GEE) logistic regression models in PROC GENMOD. As patients residing in the same

Main Place may have correlated outcomes, thus violating the assumptions of statistical independence in normal logistic models, GEE logistic regression models were used for all subsequent analysis to examine population-averaged effects of the neighborhood's socioeconomic status on HIV virologic failure, accounting for non-independence within Main Place.

Interaction terms between each neighborhood-level exposure variable and each covariate were assessed using type 3 Score tests within GEE logistic regression models, each of which only included the neighborhood-level exposure, one covariate, and the interaction term between the two. Previous work on the RFVF study and the existing literature indicate that VF and its associated risk factors may differ between men and women [16, 33, 79, 215]. Thus the correlation assessments, interaction assessment, and findings from previous work on the data were used to define the scope and main effect of interest for this analysis as that of neighborhood poverty and its interaction with gender [16].

Multivariable GEE logistic regression models examining the differential effects of neighborhood poverty between men and women on HIV virologic failure were built using a combined statistical and causal inference approach. Reference groups for each covariate were decided based on the level of each covariate with the largest number of cases for statistical efficiency. Collinearity and multicollinearity were assessed using the condition index (CI) and variance decomposition proportions (VDPs). The variables employment type and number of dependents were dropped from further analyses due to non-convergence of the model. Potential multicollinearity issues were identified among variables (excluding gender, neighborhood poverty, and the interaction term) that had CI > 30 and at least two variables had VDPs > 0.5. Variables meeting these criteria were removed sequentially until either the model's largest CI was < 30 and/or no two variables had VDPs > 0.5.

All study variables were initially considered for multivariate GEE logistic regression, if not previously excluded. After cautious consideration of the proposed DAG, mode of transportation to clinic, distance of residential address from clinic, and clinic arrival time were excluded from further analysis due to their positions as intermediates between the causal path between neighborhood socioeconomic status and virologic failure. The model selection process utilized the DAG to identify sufficient and minimally sufficient sets of variables to control for as potential confounders, and then consisted of a backwards elimination change in estimate approach from the gold standard model which contained all other covariates. The minimally sufficient set of covariates (parsimonious model) that should be controlled for according to the DAG (Figure 1) to get an unbiased estimate of the effect of neighborhood SES considering interaction with gender included: last grade of education, employment status, marital status, and age at enrollment. Variables were assessed sequentially, and dropped if the resulting change in OR for the effect of neighborhood SES on VF was $\geq$ 5% for either men or women.

Results

Patient Characteristics

Univariate analyses of all RFVF study variables for the entire 458 person cohort can be found elsewhere [26]. The distributions of covariates by case status are reported in Table 1. Of the total 458 patients enrolled in the RFVF study (158 cases and 300 unmatched controls), 438 patients were included in the final analysis according the exclusion scheme (Figure 3). The 438 patients (152 cases and 286 controls) represented 52 Main Places within the eThekwini municipality, with 266 patients (60.7%) coming from high poverty neighborhoods. Among the 438 patients included for, 35.4% were men and 92% were black Zulu (Results not shown). Ages ranged from 18 to 73 years, with a median age at enrollment of 38.4 years. The mean length of ART treatment prior to enrollment in the study was 2.5 years with 36.3% between 1 and 3 years (27.6% of cases and 40.9% of controls). Compared to controls, cases had statistically significantly greater proportions of people whose last grade of education was greater than 10th grade (88.8% cases, 76.5% controls, p = 0.0039), did not have a source of income (28.3% cases, 17.8% controls, p=0011), were unemployed (25% cases, 16.4% controls, p=0.039), a CD4 count at enrollment of < 200 cells/uL (46.4% cases, 16.8% controls, p < 0.0001), less than 35 years of age at enrollment (43.4% cases, 27.3% controls), less than 1 year on ART (46.1% cases, 22.7% controls, p< 0.0001). While cases also had statistically significantly higher proportions of people who drove a car to the study's HIV clinic and have a family pay for HIV care, it should be noted that the Chi-square test results may be unreliable with these variables that had at least one cell count of < 5 (Table 1).

Neighborhoods

Descriptive statistics for the distribution of covariates for the 438 person study cohort by neighborhood exposure status can be found in Table 2. A total of 52 Main Places from the eThekwini municipality were represented in the data, with 22 out of the 52 Main Places in the study containing only 1 or 2 study participants and one Main Place containing the maximum of 54 study participants. Figures 4 and 5 show that patients in the study appear to be more densely populated in a few Main Place, with the remainder scattered across many other Main Places. Figure 5 also shows that there is no clear difference in the spatial distribution between cases and controls. Patients lived an average of 13.7 kilometers (straight-line distance) from McCord clinic, with 84.7% of patients taking between 30 and 60 minutes to reach the clinic (of cases and of controls). The 50th percentiles for all 203 Main Places in eThekwini municipality's measures of poverty, unemployment, and incomplete education were used as thresholds to determine which neighborhoods in the study data would be categorized as "Low SES" or "High SES" neighborhoods. These thresholds corresponded to 28.9% of households living under the poverty line, 27.3% of persons who are unemployed, and 65.4% of persons with either no education or at most some secondary education respectively. Thus compared to these thresholds, the Main Places represented in our data tended to be of low poverty (30 Main Places, 172 study participants), low unemployment (32 Main Places, 229 study participants), and low incomplete education (45 Main Places, 410 study participants) (Table 2).

The frequency distributions of covariate variables remained similar, whether neighborhoods were categorized as high or low SES separately by poverty, unemployment, or education measures. Distributions for clinic arrival times, number of dependents, number of cohabitants, and distance from the clinic differed significantly between high and low poverty/unemployment neighborhoods, such that low poverty/unemployment neighborhoods tended to have greater proportions of people with short clinic arrive times, few number of dependents or cohabitants, and short distances to the clinic. Chi-square tests between all 2-variable combinations of the three neighborhood-level exposures showed very strong, statistically significant correlation poverty and unemployment ($R=0.817$, $p< 0.0001$), poverty and incomplete education ($R=0.739$, $p< 0.0001$), and unemployment and incomplete education ($R=0.776$, $p< 0.0001$). These sources of evidence combined with the sparser data when categorized study neighborhoods by eThekwini's median education values, motivated the decision to only analyze neighborhood-level poverty as the main exposure of interest for all subsequent analyses.

Regression Models

Odds ratios (ORs) comparing the bivariate associations between each covariate and case status or neighborhood-level poverty, of normal logistic regression models (Table 3) were compared with those of GEE logistic regression models (Results not shown). While normal logistic regression models assume statistical independence among individuals, GEE logistic regression models accounts for non-statistical independence of individuals coming from the same neighborhood.

There were no statistically significant ORs between any of the covariates and neighborhood-level poverty when using either normal logistic regression or GEE logistic regression. The bivariate ORs using normal logistic regression exhibited more variation than the ORs using GEE logistic regression, all of which were null (Results not shown). Similarly, after accounting for the possible lack of independence among individuals within neighborhoods using generalized estimating equations (GEE) logistic models, all univariate associations were also null.

Two multicollinearity issues were identified in the fully adjusted model when assessed sequentially. An initial issue was indicated (CI = 85.3) between income (VDP = 0.89) and payment for medication (VDPs for dummy variables = 0.86 and 0.60). Dropping the payment for medication variable from subsequent analyses led to dropping payment for medication from the model. A second multicollinearity issue was indicated (CI = 49.2) between income (VDP = 0.68) and employment status dummy variables (VDPs = 0.60 and 0.50). Income was then dropped from subsequent analyses, resulting in no more apparent multicollinearity issues. Since the DAG and supporting contextual knowledge identified the variables mode of transportation to clinic, distance of residential address from clinic, and clinic arrival time as intermediates on a directed path from neighborhood SES and virologic failure, they were excluded from consideration in any multivariate logistic regression models.

GEE logistic models were examined using a backwards elimination, change in estimate approach informed by the DAG. GEE logistic models of interest are reported in Table 4. An unadjusted GEE logistic model containing only the variables gender, neighborhood poverty, and their interaction term (Model 1) show the interaction term was statistically significant (Score test type 3 p value = 0.033). This unadjusted model (Model 1) shows that among men, those living in a low poverty neighborhood had 1.42 times greater odds of virologic failure compared to those living in a high poverty neighborhood (OR = 1.42, 95%CI: 0.79, 2.53). However when restricted to women, those living in a low poverty neighborhood had 0.77 times the odds of virologic failure compared to those living in a high poverty neighborhood (OR = 0.77, 95% CI: 0.48, 1.22). In the fully adjusted model (Model 2), the OR for residence in a low poverty neighborhood for men decreased to 1.23 (95% CI: 0.63, 2.43) while the OR for women remained similar compared to the unadjusted model (OR = 0.75, 95% CI: 0.49, 1.15). The parsimonious model controlling for the minimally sufficient set of potential confounders according to the DAG, however, did not completely control for confounding indicated by the greater than 10% change of the OR for men (OR = 1.40) (Parsimonious model not shown). Inclusion of both variables CD4 count at enrollment and years on ART to the parsimonious model changed the OR for men closer to that of the fully adjusted model (OR = 1.28; 95% CI: 0.64, 2.55), creating an adapted parsimonious model (Model 3). Following the backwards elimination change in estimate approach (> 5% change as meaningful) from Model 3 resulted in dropping all variables except for CD4 count at enrollment (OR among men adjusting for CD4 count = 1.27, 95% CI: 0.67, 2.42) (Model 4). Similar results to Model 4 occurred when the variable years on ART was added into Model 4 in place of CD4 count (OR among men = 1.29, 95% CI:0.67, 2.49; OR among women = 0.76, 95% CI: 0.48, 1.19) (Model not shown). For all GEE logistic models considered, the ORs for the effect of residence in low versus high poverty neighborhoods among women remained between 0.70 and 0.78, and all ORs of the main effect for both men and women were not statistically significant at the alpha = 0.05 level. Both the models with only CD4 count at enrollment (Model 4) and the adapted parsimonious model (Model 2) were considered as final models, based on the relationships described in the literature.

Separate analyses found that when mode of transportation to clinic, a potential mediator between neighborhood SES and VF according to the DAG, was added into either of the two final models (Model 3 and 4), the ORs for men changed meaningfully, from around 1.27 to 1.47 (Model 5 and Model 6).

Discussion

This analysis is among the first that examined the gender differences in the relationship between neighborhood socioeconomic (SES) characteristics and HIV virologic failure (VF). We found that after controlling for individual SES and clinical variables, that among men, those living in richer areas tended to have VF *more* frequently than those living in poorer areas. In contrast, we found that among women, those living in richer areas tended to have VF *less* than those living in poorer areas. This analysis also showed that mode of transportation to HIV clinic may be an important factor through which neighborhood SES is related to VF, but only for men. These findings suggest that neighborhood SES characteristics, in addition to individual SES characteristics, may have an impact on HIV VF that is different for men and women. Such findings can help in identifying appropriate interventions that consider neighborhood characteristics in order to improve HIV treatment outcomes.

The results of this analysis show that gender differences between the association of neighborhood SES and VF remain, even after accounting for individuals' SES. Prior analyses on the RFVF data found that factors related to lower SES (e.g. financial dependence) were associated with VF for women but factors related to higher SES (e.g. car ownership) were associated with VF for men. These findings support the existing literature of gender differences in ART adherence [80, 92, 202, 216], socioeconomic status as a barrier to ART adherence [18, 102, 103, 105, 106, 217], and potential gender differences in such socioeconomic factors [203, 218]. Building upon previous work examining SES at the individual level and HIV-related outcomes, our analysis showed that gender differences may also exist when SES is examined at the neighborhood level even after accounting for individual-level SES.

Even though the existing literature examining neighborhood SES effects on HIV-related health outcomes is rather sparse and inconsistent, our findings support the growing literature showing the possibility of neighborhood SES effects and gender differences in such effects on a range of health outcomes. Many of the studies using neighborhood SES measures that have found inconsistent results regarding HIV-related health outcomes used such area-based measures as proxies for individual-level SES, making conclusions regarding the neighborhoods' independent effects difficult to make [137, 138, 219, 220]. To our knowledge, only a few studies in the current HIV literature have examined the possibility of neighborhood SES effects. These studies investigated whether neighborhood SES effects persist after controlling for individual SES with regards HIV prevalence [152], HIV survival [155], and HIV viral load [154]. Two out of these three studies supported the notion of neighborhood-level SES effects after controlling for individual-level SES and clinical variables [152, 154]. Our findings were similar to that of the Shacham et. al. study, which examined three dimensions of neighborhood SES separately (e.g. per cent poverty, racial make-up, and unemployment) and found that, after accounting for individual-level SES, demographic, and clinical characteristics, there was only a weak association between viral load and neighborhood SES. This may be a reflection of the internal bias in both studies that all subjects in both samples were engaged in HIV care [154]. However, our analysis suggested that an association between neighborhood SES and VF differed between men and women, which was not considered in the Shacham et. al. study. Other non-HIV studies have shown that gender differences existed in terms of the direction and magnitude of effect for neighborhood SES measures over a range of health outcomes [117, 131, 221]. Thus, while our study may not directly relate to the study populations and questions of all of the aforementioned studies, they support the notion that contextual neighborhood effects can differ by gender, as was found in our analysis.

Our results are suggestive that the mechanisms by which neighborhood SES is related to VF for men differs from that for women. In a review, Galster synthesized the literature and summarized the mechanisms by which neighborhoods affect health into 15 distinct mechanisms under the following 4 realms:

(1) social-interactive: These mechanisms refer to social processes that are endogenous to neighborhoods, such as internal competition, relative deprivation, social cohesion, and collective socialization.

(2) environmental: These mechanisms refer to natural and human-made characteristics of the local space that may impact mental and/or physical health without impacting behaviors, such as exposure to violence, the built environment, and toxic exposure.

(3) geographical: These mechanisms refer to only spatial aspects of the neighborhood that may affect its residents' life course not due to characteristics of the neighborhood but solely because of its location "relative to larger-scale political and economic forces", such as spatial mismatch (proximity mediated by transportation networks) to employment opportunities, and public services.

(4) institutional: These mechanisms refer to actions made by those not necessarily residing inside the neighborhood but through external interface points, such as stigmatization and local institutional resources [222, 223].

These general mechanisms of neighborhood effects can apply directly to the structural barriers regarding ART adherence in low and middle income countries, such as in South Africa [146]. In regards to geographic mechanisms poorer areas are often characterized by inadequate transportation infrastructure, in terms of road networks and public transportation routes, which can be especially problematic for the portion of the population reliant on public transportation to get to HIV clinic [146, 224]. Within the cultural context of Durban, the lasting effects of apartheid era urban planning policies intended to create physical and economic isolation of townships, continue to be felt today. In many of these townships from which RFVF study patients come, there is insufficient servicing by buses or taxis, inadequate sidewalks for pedestrians, and indirect road networks from townships into Durban city central, where McCord is located [183-

185, 194]. With regards to environmental barriers, repeated exposure to community violence that is characteristic of many poorer townships in South Africa following the disruption of social cohesion from apartheid, may negatively impact adherence through increased depression or personal stress in such environments [26, 204]**.** Social-interactive and institutional neighborhood mechanisms through which ART adherence and VF can be impacted may related to the prevailing HIV stigma and discrimination that may influence skipping pills, avoiding clinic visits, traveling long distances for anonymous treatment, and other reasons for sub-optimal adherence [92, 222, 225].

We hypothesize that our results, that men living in *richer* areas and women living in *poorer* areas have a greater tendency for VF, are related to how gender-specific HIV stigmas are upheld in neighborhoods of different socioeconomic statuses. We consider that gender power disparities in different neighborhood types may explain why among women, those living in poor neighborhoods tended to have worse outcomes than those in richer neighborhoods even after accounting for individual SES, results which support those found in the literature [153, 226]. While both men and women experience HIV-related stigmas, women may be especially targeted due to already existing stigmas and inequalities related to gender in many settings [148, 220, 227]. Gender power disparities within communities can fuel women-specific HIV stigmas of women being blamed more easily for HIV infection, accused of having extramarital sex, or being perceived as sex workers [92, 220, 227, 228]. These disparities can also relate to how in many settings, women tend to be more financially dependent than men, as was also shown in previous analyses of the RFVF data [16, 92]. Settings where gender-power inequalities are especially pervasive may exacerbate the amount of HIV-related stigma women experience and result in women not disclosing their HIV status, hiding their medications or taking them inconsistently for fear of disclosure, and other actions that reduce optimal ART adherence [220]. Thus, our results that show women who live in poorer neighborhoods being more likely to have VF may be linked to the notion that gender-power disparities are more pervasive and impact ART adherence more greatly in poorer neighborhoods compared to richer neighborhoods [203].

A social-interactive mechanism that may explain why among men, those who live in richer areas are more likely to have VF, is that of hegemonic masculinity. The majority of the patients in the whole RFVF cohort are black Zulu (92%) as is most of the eThekwini municipality [229]. The Zulu culture is one that values strength and traditional gender roles, which in modern times may translate into male expectations to marry, work hard, and provide for the family [16, 230]. In such environments where ideals of masculinity prevail, men's adherence to ART may be greatly impacted by reluctance of accepting the "sick role", a desire to protect reputation and respectability, and a societal expectation to fulfill economic family responsibilities [80, 228, 231]. The community stigma against HIV-positive men, which includes perceptions of weakness for carrying a "woman's disease" in many low and middle income countries, also plays a role in men's resistance in admitting illness, seeking timely care, leaving work for HIV-related appointments, and consistent adherence in the home or workplace [92, 228, 231]. It has been cited that ideals of hegemonic masculinities are linked to privileged social classes, particularly in urban Southern African settings, where ideals of masculinity may fuel greater competition and value placed on social status among the more privileged social classes [94, 230, 232, 233].

Assuming the DAG presented in Figure 1 is correct, it suggests that car ownership may be a mediator for the relationship between neighborhood SES and VF, and our empirical evidence further suggests that this relationship may be dependent on gender. If car ownership is indeed a mediator for men, it may represent either a geographic mechanism, such that car ownership measures ease of access to the clinic by neighborhood, or a social-interactive mechanism, such that car ownership measures masculinity ideals by neighborhood. Analyses on the RFVF dataset provide stronger evidence for the latter. Separate univariate analyses were conducted in both the current and previous work with the RFVF dataset to further characterize the men and women subpopulations by individual-level and neighborhood-level socioeconomic characteristics, and potential transportation-related mediators, as indicated in the DAG (Figure 1) **[**16**].** Previous work on the RFVF dataset found that men tended to have more car ownership than women, and that male car ownership tended to be associated with marriage, having income, being self-employed, owning a home, and being educated beyond 9 years – characteristics that conceptually match that of the ideals of masculinity [16, 234]. We additionally found that while men were distributed nearly 40% and 60% in rich and poor neighborhoods respectively, that rich neighborhoods tended to be closer to the clinic and have shorter arrival times, and the distribution of car ownership for men was nearly the same between rich and poor neighborhoods. Therefore, since including/excluding mode of transportation in the final model changed how neighborhood SES was related to VF meaningfully for men, this provides further support to the notion of car ownership as an indicator of how hegemonic masculinity may influence VF for men differently between rich and poor areas. However, further analyses would be needed to confirm the hypothesis of an independent effect of car ownership for men. The concept of car ownership as a symbol for masculinity has been noted in other cultures [16, 221, 235, 236], particularly in how it may influence HIV care [16, 236, 237]**.** It should be noted that these conclusions are under the assumption of a correct DAG. If in fact the DAG was misspecified, the meaningful change in estimate from the final model to one that includes mode of transportation may be a result of controlling for real confounding or inducing collider bias.

Our analysis also showed that higher individual-level SES was not as strongly associated with higher neighborhood-level SES as may have been anticipated, and vice versa. In Shacham et. al.'s study of 762 individuals within 273 census tracts, poorer neighborhoods had statistically significantly more individuals with ≤ $10,000 annual income and ≤ complete high school education than richer neighborhoods [154]. The existing literature similarly provides evidence that those with resources have greater residential mobility and will tend to seek out richer, "nicer" neighborhoods [129]. Our results can therefore be explained by (a) the difference between what makes a neighborhood "rich" or "poor" in our analysis is smaller than it may be in other studies, or (b) there are more important factors, independent of individual-SES, at play that have determined where people live in Durban. It is plausible that the neighborhoods in our study are relatively similar, given that the external definitions of rich/poor were based on eThekwini standards of poverty, which has been shown to be rather homogenous especially when compared to the rest of the Kwa-ZuluNatal province [238]. The second explanation is plausible if one considers that residential mobility within Durban may be more greatly impacted by cultural factors, independent of SES. Such cultural factors may include the voluntary decisions to live in areas close to family and others of similar culture [239, 240]**,** or the involuntary decisions to live in certain areas as a result of gentrification and/or forced residential segregation during and post-apartheid [241]. It should also be noted that since HIV patients attending McCord Hospital are a select group of patients, they may not be representative of the population within these neighborhoods overall.

Additionally, we found through our model selection process that controlling for the study's potential confounders as defined by the DAG and contextual knowledge provided similar results as when only CD4 count at enrollment was controlled for among both men and women. Previous literature supports individual-level SES associations between both VF/ART adherence [102, 103, 109] and neighborhood-level SES [242, 243]. It should be noted that although our data did not show significant or strong associations between VF and many of the study's potential confounders, this does not necessarily imply that no association exists. CD4 count at enrollment exhibited the relatively most significant univariate association with VF. It should be noted, however, that the meaningful change in estimate whether CD4 count at enrollment was controlled for or not only to applied men, as women's OR between neighborhood SES and VF remained close to 0.7 for all models considered. One plausible explanation for the stability of the women's

ORs across all models in our analysis contrasted to the relative instability of that of men's is due to the overrepresentation of women compared to men in our study (64.6% vs. 35.4% respectively), and that the change in estimate observed is a result of sparse data.

Strengths

One of the key strengths of this analysis is the utilization of generalized estimating equation (GEE) logistic regression models to account for the clustering of individuals within the same Main Places. Ignoring the non-independence of the subjects living in the same Main Place by using a normal logistic regression model would have resulted in biased measures of association, as indicated in Table 3. Compared to conditional multilevel models, GEE models require fewer assumptions (primarily only that of MCAR – missing data are random samples of all persons in each neighborhood), are particularly robust to misspecified working correlations, and can still examine cross-level interactions, as is done in this analysis [244, 245]**.** Another strength of the current analysis is the careful consideration of causal relationships between covariates in order to make informed decisions about which variables would be most appropriate to control for that would not result in opening backdoor biasing paths. The thorough development of a DAG based on contextual knowledge and supported by these results allow for more meaningful interpretations of results. Similarly, basing the backwards elimination model selection process on meaningful changes in estimate of the gender stratum-specific ORs (i.e. > 5% changes) rather than purely statistical significance is potentially a more appropriate approach for identifying confounders.

Limitations

One potential limitation to the analysis is misclassification bias of the binary neighborhood-level poverty exposure variable. Neighborhood poverty level was acquired from the 2011 South Africa Census, which displayed data as counts of people per Main Place within 12 strata of income ranges. The process of defining the poverty threshold as R9,600 (nearly R2,000 higher than the published national poverty line), producing continuous proportions of each Main Place's degree of poverty from percentage of households under the poverty line, and categorizing these continuous proportions of the Main Places in the study into "low poverty" and "high poverty" neighborhoods based eThekwini's median poverty levels may not have represented the true nature of the data. Furthermore, the speculations made in this analysis regarding the causal mechanisms through which neighborhood SES impacts VF for men and women are limited both by the lack of temporality within a case-control study design and the lack of neighborhood-level covariates that could be incorporated into the models for a mediation analysis. Another limitation includes the potential misclassification of individuals to Main Places by the geocoding process. Since many exact addresses were not provided and several discrepancies existed in the Main Places names between census tabular data and GIS files which required manual re-matching, it is possible for some individuals to have been incorrectly categorized into a Main Place of a different poverty level. Lastly, even though the entire RFVF cohort was powered appropriately, a loss of statistical power from exclusion of individuals through the geocoding process and the stratification by gender may have caused the lack of statistical significance often seen in this analysis [16]. Other strengths and limitations specific to the RFVF study are described elsewhere [26].

Future Directions

While the current analysis sheds light on the potential impact of neighborhood SES on VF in men and women, additional analyses should be done to further understand this relationship. The next immediate analysis should be to conduct a more thorough mediation analysis to determine if travel-related variables (distance to clinic, mode of transportation, time to arrive to clinic) are potential mechanisms through which neighborhood SES affects VF. Given the results of the current analysis, neighborhood-level indicators of community HIV stigma may be of particular interest. Additional analyses could also assess whether the relationships of neighborhood SES on VF for men and for women change across space. The current analysis assumes that the effect of a relatively poor neighborhood that is next to McCord exerts the same degree of effect than a similarly poor neighborhood that is over 20 kilometers away from McCord. A test of the sensitivity of such assumptions could be implemented with geographically weighted regression and could provide critical information to further understand the degree to which potential neighborhood effects operate through social mechanisms and/or geographic mechanisms. However, the small sample size in the RFVF study may be an obstacle to performing geographic weighted regression on these data. Other related analyses of interest may include operationalizing some of the variables in this sub-study differently to more closely represent such variables' complexities, such as measuring neighborhood-level SES as a continuous measure, replacing individual-level income with a wealth index previously constructed from the RFVF data [16], or using Manhattan (i.e. network analysis) distance rather than Euclidean (i.e. straight-line) distance from each place of residence to McCord Hospital. As the current analysis assumed the social process of neighborhood poverty operated at the Main Place level, it may be of interest to examine neighborhood SES as defined by lower South African geographic frames, such as the Sub Place level (Figure 2).

Conclusion

This analysis suggests that neighborhood socioeconomic characteristics may have an impact on HIV virologic failure (VF) that goes beyond individual socioeconomic characteristics and that differs between men and women. Specifically, our data indicates that among men, those living in *richer* neighborhoods are more likely to have VF, while among women, those living in *poorer* neighborhoods are more likely to have VF. Similar results are obtained whether we control for literature supported potential confounders or just for CD4 count at enrollment. We postulate that these neighborhood effects could be related to how among men and among women, HIV-stigma and gender roles residents of poorer versus richer neighborhoods differently. Our results and related literature support that traditional gender power dynamics that hinder women's abilities to adhere to ART may be more pervasive in poorer regions, while ideals of masculinity that hinder men's abilities to adhere to and access ART may be more pervasive in richer regions. In order to develop the deeper story of how individual-level risk factors lead to HIV virologic failure, it will become increasingly crucial to consider such factors in their sociocultural contexts to understand how community-level attributes also fit into this story. Thus neighborhood-level exposures should be considered in future investigations of risk factors for poor adherence and virologic failure.

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Tables and Figures

Table 1. Frequency distributions of RFVF patient characteristics by Case status

	Total (n=438)		Cases (n= 152)		Controls (n= 286)		p value[k]
	No.	%[a]	No.	%[a]	No.	%[a]	
Gender	438		152		286		
Male	155	35.4	72	47.4	83	29.0	0.0001
*Female	283	64.6	80	52.6	203	71.0	
Last grade of education							
0 to 6	36	8.2	5	3.3	31	10.8	0.0039
7 to 9	49	11.2	12	7.9	37	12.9	
*10 to 12	353	80.6	135	88.8	218	76.2	
Source of income							
No	94	21.5	43	28.3	51	17.8	0.0112
*Yes	344	78.5	109	71.7	235	82.2	
Employment status							
Unemployed[b]	85	19.4	38	25.0	47	16.4	0.0397
*Employed[c]	317	72.4	106	69.7	211	73.8	
Other[d]	36	8.2	8	5.3	28	9.8	
Employment Type							
*Basic	218	68.6	75	71.4	143	67.1	0.0690
Skilled	72	22.6	17	16.2	55	25.8	
Professional	28	8.8	13	12.4	15	7.0	
Missing	120		47		73		
Living arrangement							
Own a house	161	36.8	47	30.9	114	39.9	0.1502
Rent	58	13.2	20	13.2	38	13.3	
*Dependent living[e]	219	50.0	85	55.9	134	46.9	
Mode of Transport[f]							
Car	58	13.3	30	19.7	28	9.8	0.004[m]
*Mini-Bus/Bus	369	84.4	121	79.6	248	87.0	
Other	10	2.3	1	0.7	9	3.2	
Missing	1				1		
Clinic Arrival Time							
< 30 minutes	37	8.5	15	9.9	22	7.7	0.5784
*30 - 60 minutes	371	84.7	125	82.2	246	86.0	
> 60 minutes	30	6.9	12	7.9	18	6.3	
Pay for care[g]							
*Self-pay	346	79.0	112	73.7	234	81.8	0.0138[m]
Family Member	83	19.0	39	25.7	44	15.4	
Other[h]	9	2.1	1	0.7	8	2.8	
Marital status							
Not in a relationship[i]	154	35.2	40	26.3	114	39.9	0.0047

*In a relationship[j]	284	64.8	112	73.7	172	60.1	
CD4 Count at Enrollment (cells/uL)[k]							
*< 200	118	27.1	70	46.4	48	16.8	<0.0001
200 - 350	135	31.0	46	30.5	89	31.2	
350 - 500	98	22.5	19	12.6	79	27.7	
>= 500	85	19.5	16	10.6	69	24.2	
Missing	2		1		1		
Number of dependents							
0 to 2	112	32.0	35	31.5	77	32.2	0.9815
*3 to 5	155	44.3	49	44.1	106	44.4	
> 5	83	23.7	27	24.3	56	23.4	
Missing	88		41		47		
Number of cohabitants							
0 to 2	114	26.0	41	27.0	73	25.5	0.6299
*3 to 5	215	49.1	70	46.1	145	50.7	
> 5	109	24.9	41	27.0	68	23.8	
Age at enrollment (yrs)							
*< 35	144	32.9	66	43.4	78	27.3	0.0006
35 to 42	146	33.3	50	32.9	96	33.6	
> 42	148	33.8	36	23.7	112	39.2	
Distance from clinic (km)							
< 10	136	31.1	45	29.6	91	31.8	0.7089
*10 to 20	227	51.8	78	51.3	149	52.1	
> 20	75	17.1	29	19.1	46	16.1	
Years on ART							
*< 1	135	30.8	70	46.1	65	22.7	<0.0001
1 to 3	159	36.3	42	27.6	117	40.9	
> 3	144	32.9	40	26.3	104	36.4	

[a] Column percents, excluding Missings

[b] "Unemployed" includes those who are unemployed and seeking work, and those who are unemployed and NOT seeking work

[c] "Employed" include those who are employed full-time, part-time, or self-employed

[d] Other includes: "disabled", "student", "retired", and two individuals who indicated 2 categories: 1) "disabled" and "retired", 2) "student" and "employed part-time"

[e] "Dependent living" indicates a dependent living situation defined as staying with family, friends, employer, or other

[f] "Mode of Transport" indicates mode of transportation used to attend appointments at McCord's HIV clinic

[g] "Pay for Care" indicates who pays for the HIV medications and care for the individual

[h] "Other" includes: HIV medications and care are paid by a grant, sponsor, employer, or other

[i] "Not in a relationship" includes individuals who are divorced, single with no partners, widowed, or separated

[j] "In a relationship" includes individuals who are married, single and living with partner, or single and not living with partner

[k] p value for Chi-squared statistical significance

[m] ≥ 1 cell count less than 5. Excluding group with sparse data maintains statistical signficance ($p < 0.05$)

* = Reference group

Table 2. Frequency distributions of RFVF patients (n) within Main Places (N) by Neighborhood-level Exposures

	% Households under Poverty Line[l]					% Persons Unemployed[m]					% Persons Incomplete Education[n]				
	Low Poverty (N=30, n=172)[o]		High Poverty (N=22, n=266)[o]			Low Unemployment (N=32, n=229)[o]		High Unemployment (N=20, n=209)[o]			Low Incomplete Education (N=45, n=410)[o]		High Incomplete Education (N=7, n=28)[o]		
	No.	**%[a]**	**No.**	**%[a]**	***p*[k]**	**No.**	**%[a]**	**No.**	**%[a]**	***p*[k]**	**No.**	**%[a]**	**No.**	**%[a]**	***p*[k]**
Case/Control Status															
Case	59	34.3	93	35.0	0.89	75	32.8	77	36.8	0.37	138	33.7	14	50.0	0.08
*Control	113	65.7	173	65.0		154	67.3	132	63.2		272	66.3 4	14	50.0	
Gender															
Male	60	34.9	95	35.7	0.86	73	31.9	82	39.2	0.11	143	34.9	12	42.9	0.39
*Female	112	65.1	171	64.3		156	68.1	127	60.8		267	65.1	16	57.1	
Last grade of education															
0 to 6	19	11.1	17	6.4	0.22	21	9.2	15	7.2	0.69	34	8.3	2	7.1	0.51
7 to 9	18	10.5	31	11.7		24	10.5	25	12.0		44	10.7	5	17.9	
*10 to 12	135	78.5	218	82.0		184	80.4	169	80.9		332	81.0	21	75.0	
Source of income															
No	41	23.8	53	19.9	0.33	53	23.1	41	19.6	0.37	86	21.0	8	28.6	0.34
*Yes	131	76.2	213	80.1		176	76.9	168	80.4		324	79.0	20	71.4	
Employment status															
Unemployed[b]	35	20.4	50	18.8	0.86	44	19.2	41	19.6	0.99	77	18.8	8	28.6	0.45
*Employed[c]	122	70.9	195	73.3		166	72.5	151	72.3		299	72.9	18	64.3	
Other[d]	15	8.7	21	7.9		19	8.3	17	8.1		34	8.3	2	7.1	
Employment Type															
*Basic	80	66.1	138	70.1	0.03	107	64.5	111	73.0	0.03	203	67.7	15	83.3	0.27

Skilled	35	28.9	37	18.8		47	28.3	25	16.5		69	23.0	3	16.7	
Professional	6	5.0	22	11.2		12	7.2	16	10.5		28	9.3	0	0.0	
Missing	51		69			63.0		57			110		10		
Living arrangement															
Own a house	59	34.3	102	38.4	0.68	82	35.8	79	37.8	0.42	150	36.6	11	39.3	0.29
Rent	23	13.4	35	13.2		35	15.3	23	11.0		57	13.9	1	3.6	
*Dependent living[e]	90	52.3	129	48.5		112	48.9	107	51.2		203	49.5	16	57.1	
Mode of Transport[f]															
Car	21	12.2	37	14.0	0.0004	28	12.3	30	14.4	0.0083	56	13.7	2	7.1	0.41
*Mini-Bus/Bus	141	82.0	228	86.0		190	83.3	179	85.7		343	83.9	26	92.9	
Other	10	5.8	0	0.0		10	4.4	0	0.0		10	2.4	0	0.0	
Missing			1			1					1				
Clinic Arrival Time															
< 30 minutes	23	13.4	14	5.3	0.009	33	14.4	4	1.9	<0.0001	37	9.0	0	0.0	0.08
*30 - 60 minutes	136	79.1	235	88.4		185	80.8	186	89.0		347	84.6	24	85.7	
> 60 minutes	13	7.6	17	6.4		11	4.8	19	9.1		26	6.3	4	14.3	
Pay for care[g]															
*Self-pay	130	75.6	216	81.2	0.007	177	77.3	169	80.9	0.08	326	79.5	20	71.4	0.32
Family Member	34	19.8	49	18.4		44	19.2	39	18.7		75	18.3	8	28.6	
Other[h]	8	4.7	1	0.4		8	3.5	1	0.5		9	2.2	0	0.0	
Marital status															
Not in a relationship[i]	67	39.0	87	32.7	0.18	89	38.9	65	31.1	0.09	145	35.4	9	32.1	0.73
*In a relationship[j]	105	61.1	179	67.3		140	61.1	144	68.9		265	64.6	19	67.9	
CD4 Count at Enrollment (cells/ uL)[k]															
*< 200	52	30.2	66	25.0	0.37	62	27.1	56	27.1	0.72	108	26.5	10	35.7	0.56
200 - 350	49	28.5	86	32.6		67	29.3	68	32.9		126	30.9	9	32.1	
350 - 500	34	19.8	64	24.2		51	22.3	47	22.7		92	22.6	6	21.4	

>= 500	37	21.5	48	18.2		49	21.4	36	17.4		82	20.1	3	10.7	
Missing			2					2			2				
Number of dependents[k]															
0 to 2	50	37.6	62	28.6	0.05	66	36.7	46	27.1	0.05	108	32.7	4	20.0	0.05
*3 to 5	60	45.1	95	43.8		80	44.4	75	44.1		141	42.7	14	70.0	
> 5	23	17.3	60	27.7		34	18.9	49	28.8		81	24.6	2	10.0	
Missing	39		49			49		39			80		8		
Number of cohabitants[k]															
0 to 2	51	29.7	63	23.7	0.002	67	29.3	47	22.5	0.0004	109	26.6	5	17.9	0.50
*3 to 5	94	54.7	121	45.5		123	53.7	92	44.0		201	49.0	14	50.0	
> 5	27	15.7	82	30.8		39	17.0	70	33.5		100	24.4	9	32.1	
Age at enrollment (yrs)															
*< 35	55	32.0	89	33.5	0.72	79	34.5	65	31.1	0.71	137	33.4	7	25.0	0.50
35 to 42	55	32.0	91	34.2		76	33.2	70	33.5		134	32.7	12	42.9	
> 42	62	36.1	86	32.3		74	32.3	74	35.4		139	33.9	9	32.1	
Distance from clinic (km)															
< 10	93	54.1	43	16.2	<0.0001	125	54.6	11	5.3	<0.0001	136	33.2	0	0.0	0
*10 to 20	47	27.3	180	67.7		80	34.9	147	70.3		206	50.2	21	75.0	
> 20	32	18.6	43	16.2		24	10.5	51	24.4		68	16.6	7	25.0	
Years on ART															
*< 1	56	32.6	79	29.7	0.39	75	32.8	60	28.7	0.32	128	31.2	7	25.0	0.70
1 to 3	66	38.4	93	35.0		86	37.6	73	34.9		149	36.3	10	35.7	
> 3	50	29.1	94	35.3		68	29.7	76	36.4		133	32.4	11	39.3	

[a] Column percents, excluding Missings

[b] "Unemployed" includes those who are unemployed and seeking work, and those who are unemployed and NOT seeking work

[c] "Employed" include those who are employed full-time, part-time, or self-employed

[d] Other includes: "disabeled", "student", "retired", and two individuals who indicated 2 categories:

1) "disabeled" and "retired", 2) "student" and "employed part-time"

[e] "Dependent living" indicates a dependent living situation defined as staying with family, friends, employer, or other

[f] "Mode of Transport" indicates mode of transportation used to attend appointments at McCord's HIV clinic

[g] "Pay for Care" indicates who pays for the HIV medications and care for the individual

[h] "Other" includes: HIV medications and care are paid by a grant, sponsor, employer, or other

[i] "Not in a relationship" includes individuals who are divorced, single with no partners, widowed, or separated

[j] "In a relationship" includes individuals who are married, single and living with partner, or single and not living with partner

[k] p value for Chi-squared statistical significance

[l] "% Households Under Poverty Line" is the percent of households in each Main Place earning < R9,600 per year, approximately corresponding to the national uppoer poverty line of R7,440

[m] "% Persons Unemployed" is the percent of persons ≥ 15 years self-reported as unemployed or discouraged work seeker

[n] "% Persons Incomplete Education" is the percent of persons ≥ 20 years with either no schoolding or at most some secondary

[o] Categorization thresholds derived from the median value of the 203 Main Places in eThekwini for each exposure variable; N= number of Main Places; n=number of individuals

* = Reference group

Table 3. Crude Odds Ratios (ORs) between each Covariate and Case status or Neighborhood-level Exposures (Normal Logistic Regression)

	Case				% Households Under Poverty Line[c]			
	OR[a]	CI_{Lower}	CI_{Upper}	$Width_m$	OR[b]	CI_{Lower}	CI_{Upper}	$Width_m$
Gender								
Male	2.20	1.68	2.89	1.72	1.04	0.69	1.55	2.23
*Female	1.00	––	––	––	1.00	––	––	––
Last grade of education								
0 to 6	0.26	0.10	0.67	6.69	0.55	0.28	1.10	3.96
7 to 9	0.52	0.34	0.81	2.38	1.07	0.57	1.98	3.45
*10 to 12	1.00	––	––	––	1.00	––	––	––
Source of income								
No	1.82	1.27	2.63	2.07	0.80	0.50	1.26	2.52
*Yes	1.00	––	––	––	1.00	––	––	––
Employment status								
Unemployed[d]	1.63	1.03	2.57	2.49	0.89	0.55	1.46	2.65
*Employed[e]	1.00	––	––	––	1.00	––	––	––
Other[f]	0.57	0.25	1.29	5.20	0.88	0.43	1.76	4.06
Employment Type								
*Basic	1.00	––	––	––	1.00	––	––	––
Skilled	0.59	0.33	1.07	3.28	0.61	0.36	1.05	2.93
Professional	1.65	0.68	4.00	5.85	2.13	0.83	5.46	6.60
Living arrangement								
Own a house	0.65	0.42	1.00	2.40	1.21	0.79	1.83	2.31
Rent	0.83	0.45	1.51	3.36	1.06	0.59	1.92	3.26
*Dependent living[g]	1.00	––	––	––	1.00	––	––	––
Clinic Transport[h]								
Car	2.19	1.30	3.70	2.85	1.09	0.61	1.94	3.16
*Mini-Bus/Bus	1.00	––	––	––	1.00	––	––	––
Other	0.23	0.02	3.06	184.30	0.00	0.00	No est.	
Clinic Arrival Time								
< 30 minutes	1.33	0.65	2.72	4.15	0.35	0.18	0.71	4.03
*30 - 60 minutes	1.00	––	––	––	1.00	––	––	––
> 60 minutes	1.32	0.62	2.82	4.57	0.76	0.36	1.61	4.50
Pay for care[i]								
*Self-pay	1.00	––	––	––	1.00	––	––	––
Family Member	1.87	1.32	2.66	2.01	0.87	0.53	1.41	2.66
Other[j]	0.26	0.04	1.74	45.04	0.08	0.01	0.61	65.42

Marital status								
Not in a relationship[k]	0.54	0.34	0.85	2.51	0.76	0.50	1.14	2.26
*In a relationship[l]	1.00	––	––	––	1.00	––	––	––
CD4 Count at Enrollment (cells/ uL)								
*< 200	1.00	––	––	––	1.00	––	––	––
200 - 350	0.36	0.22	0.56	2.53	1.38	0.83	2.29	2.75
350 - 500	0.16	0.09	0.30	3.33	1.48	0.85	2.58	3.02
>= 500	0.16	0.09	0.29	3.23	1.02	0.58	1.79	3.08
Number of dependents								
0 to 2	0.98	0.53	1.81	3.40	0.78	0.48	1.28	2.68
*3 to 5	1.00	––	––	––	1.00	––	––	––
> 5	1.04	0.61	1.80	2.97	1.65	0.92	2.94	3.19
Number of cohabitants								
0 to 2	1.17	0.66	2.05	3.08	0.96	0.61	1.52	2.49
*3 to 5	1.00	––	––	––	1.00	––	––	––
> 5	1.25	0.80	1.96	2.44	2.36	1.41	3.94	2.78
Age at enrollment (yrs)								
*< 35	1.00	––	––	––	1.00	––	––	––
35 to 42	0.61	0.35	1.08	3.10	1.02	0.64	1.64	2.58
> 42	0.37	0.24	0.58	2.44	0.86	0.54	1.37	2.55
Distance from clinic (km)								
< 10	0.94	0.64	1.37	2.14	0.12	0.07	0.20	2.63
*10 to 20	1.00	––	––	––	1.00	––	––	––
> 20	1.20	0.66	2.19	3.31	0.35	0.20	0.61	3.06
Years on ART								
*< 1	1.00	––	––	––	1.00	––	––	––
1 to 3	0.33	0.21	0.54	2.59	1.00	0.63	1.59	2.54
> 3	0.36	0.24	0.52	2.14	1.33	0.82	2.16	2.64

[a] OR comparing Case vs. Control (reference)

[b] OR comparing Low poverty vs. High poverty (reference)

[c] "% Households Under Poverty Line" is the percent of households in each Main Place earning < R9,600 per year, approximately corresponding to the national uppoer poverty line of R7,440

[d] "Unemployed" includes those who are unemployed and seeking work, and those who are unemployed and NOT seeking work

[e] "Employed" include those who are employed full-time, part-time, or self-employed

[f] Other includes: "disabeled", "student", "retired", and two individuals who indicated 2 categories: 1) "disabeled" and "retired", 2) "student" and "employed part-time"

[g] "Dependent living" indicates a dependent living situation defined as staying with family, friends, employer, or other

[h] "Mode of Transport" indicates mode of transportation used to attend appointments at McCord's HIV

clinic

[i] "Pay for Care" indicates who pays for the HIV medications and care for the individual

[j] "Other" includes: HIV medications and care are paid by a grant, sponsor, employer, or other

[k] "Not in a relationship" includes individuals who are divorced, single with no partners, widowed, or separated

[l] "In a relationship" includes individuals who are married, single and living with partner, or single and not living with partner

[m] OR Width calculated as Upper limit divided by Lower limit
* = Reference group

Table 4. Summary of Gender-specific effects (Low Neighborhood Poverty vs. High Neighborhood Poverty on Virologic Failure) of Multivariable GEE Logistic Regression Models

Model	Variables in the Model	Gender-specific effects			
		M/F	OR	95% CI_L	95% CI_H
Model 1: Unadjusted	(1)Neighborhood Poverty (2)Gender (3)Neighborhood Poverty*Gender interaction	M	1.42	0.79	2.53
		F	0.76	0.48	1.22
Model 2: Fully Adjusted	(1)Neighborhood Poverty (2)Gender (3)Neighborhood Poverty*Gender interaction (4)Last grade of Education (5)Employment status (6)Living arrangement (7)Marital status (8)Number of cohabitants (9)Age at enrollment (10) CD4 count at enrollment (11)Years on ART	M	1.23	0.63	2.43
		F	0.75	0.49	1.15
Model 3: Adapted Parsimonious	(1)Neighborhood Poverty (2)Gender (3)Neighborhood Poverty*Gender interaction (4) Last grade of Education (5) Employment status (6) Marital status (7) Age at enrollment (8) CD4 count at enrollment (9) Years on ART	M	1.28	0.64	2.55
		F	0.74	0.48	1.16
Model 4: Only CD4 count at enrollment	(1)Neighborhood Poverty (2)Gender (3)Neighborhood Poverty*Gender interaction (4) CD4 count at enrollment	M	1.27	0.67	2.42
		F	0.73	0.45	1.19
Model 5: Adapted Parsimonious + Mode of transport	(1)Neighborhood Poverty (2)Gender (3)Neighborhood Poverty*Gender interaction (4) Last grade of Education (5) Employment status (6) Marital status (7) Age at enrollment (8) CD4 count at enrollment (9) Years on ART (10) Clinic Transport	M	1.47	0.76	2.83
		F	0.75	0.49	1.17
Model 6: Only CD4 count at enrollment + Mode of transport	(1)Neighborhood Poverty (2)Gender (3)Neighborhood Poverty*Gender interaction (4) CD4 count at enrollment (5) Mode of Transport	M	1.47	0.79	2.70
		F	0.75	0.46	1.21

Figure 1. Directional acyclic graph (DAG) relating study exposure (Neighborhood SES), outcome (VF), and covariates

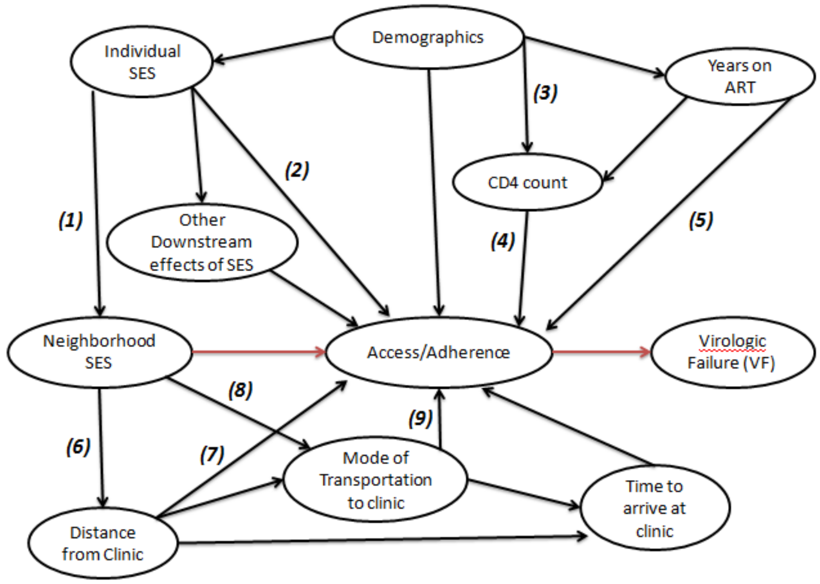

Figure 1. The above directed acyclic graphs (DAG) assists in visualizing proposed causal relationships and confounding pathways through which Neighborhood SES (the exposure) may impact HIV VF (the outcome). Access/adherence to ART is an important cause of VF [49, 50, 109, 246], and can be impacted by individual SES (employment, income, and education) [67, 102, 103, 109, 121, 125], downstream effects of SES such as dependent living arrangement and number of cohabitants [102, 247, 248], demographics such as gender, age, and marital status [102, 111, 123, 126, 249], CD4 at enrollment [111, 115], and Years on ART treatment [87-89].

(1) Individual SES can determine Neighborhood SES as wealthier individuals can have more resources to be able to move into richer neighborhoods [242, 243]. **(2)** Individual SES and ART access/adherence can be explained by two competing theories; on one hand, individuals with higher SES tend to have more stable living conditions and greater ability to pay for medications and transportation to clinic, promoting optimal ART adherence [103, 105]; on the other hand individuals with higher SES may be too busy to pick up or take ART pills regularly, be more weary of the side effects of a lifelong regimen, or be more weary of stigma [74, 102, 124]. **(3)** Women can have higher CD4 counts than men because of higher rates of HIV-testing and repeat testing, higher acceptance of linkage to care and slower CD4 decline among HIV-infected individuals, and because of other biologic reasons among non-infected individuals [250, 251]. **(4)** CD4 count is used as a measure of disease severity, and those with lower CD4 count tend to be sicker and possibly less able to adhere to medications and pick up medications on time. **(5)** The more time a person has spent adhering to treatment, the more likely he/she is able to maintain adherence, possibly due to the establishment of routines to promote adherence.

The bottom half of the DAG shows the relationship of neighborhood SES and mode of transportation to clinic [135, 252, 253] and its interrelationships with distance [102] and time to travel to the clinic[109, 224]. **(6)** Poorer neighborhoods, particularly in KwaZulu-Natal, tend to be more rural and further away from the urban clinics in Durban [238, 254]. **(7)** Living far away from clinic in poorer neighborhoods may reduce access/adherence through increased costs of travel and less adequate road networks, while living close to clinic may reduce access/adherence from stigma and fear of being seen visiting an HIV clinic [102, 183, 194]. **(8)** Poorer neighborhoods are also more likely to have less cars, which are not affordable for the poorest individuals, and be inadequately serviced by public transportation options [183, 185]. **(9)** Owning a car as mode of transportation can either increase access/adherence allowing the individual to attend clinic around his/her schedule but can also decrease access/adherence if it is a marker for neighborhood-level stigma of receiving HIV treatment [16].

Figure 2. Hierarchy of graphic frames used by Statistics South Africa (Census 2011)

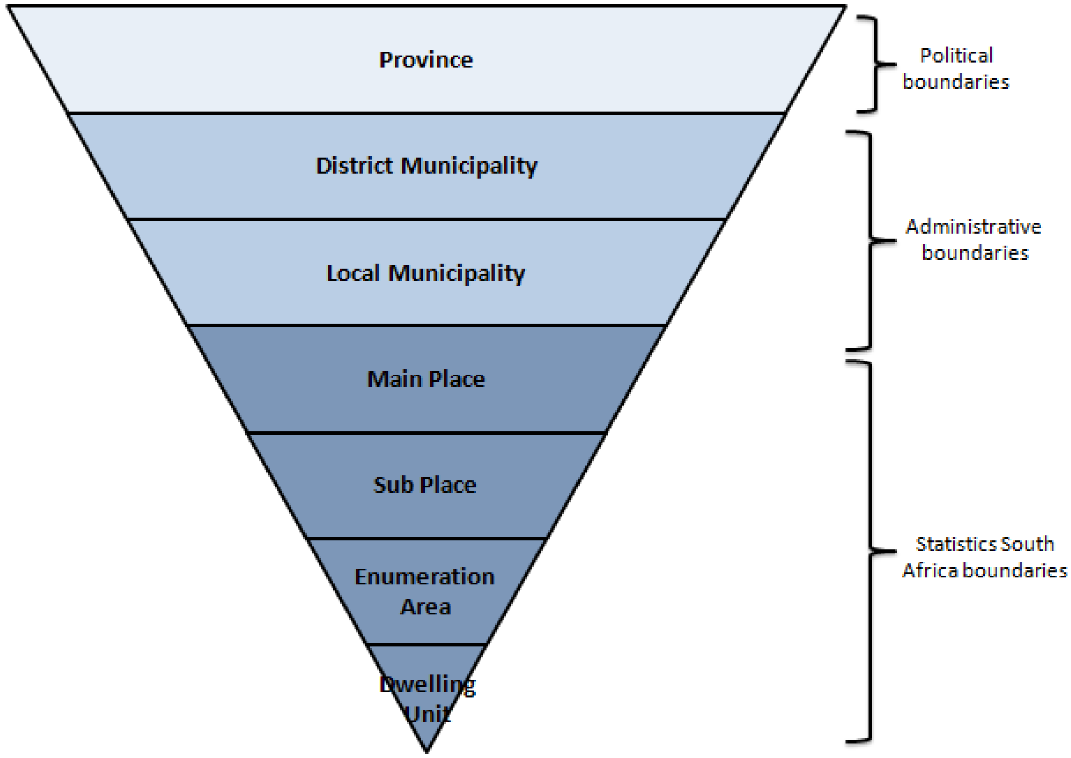

Figure 2. The above diagram shows the hierarchical structures of geographical entities within the South African 2011 Census. Neighborhood in this analysis was defined at the Main Place level.

Figure 3. Exclusion scheme for current analysis from total cohort of RFVF study

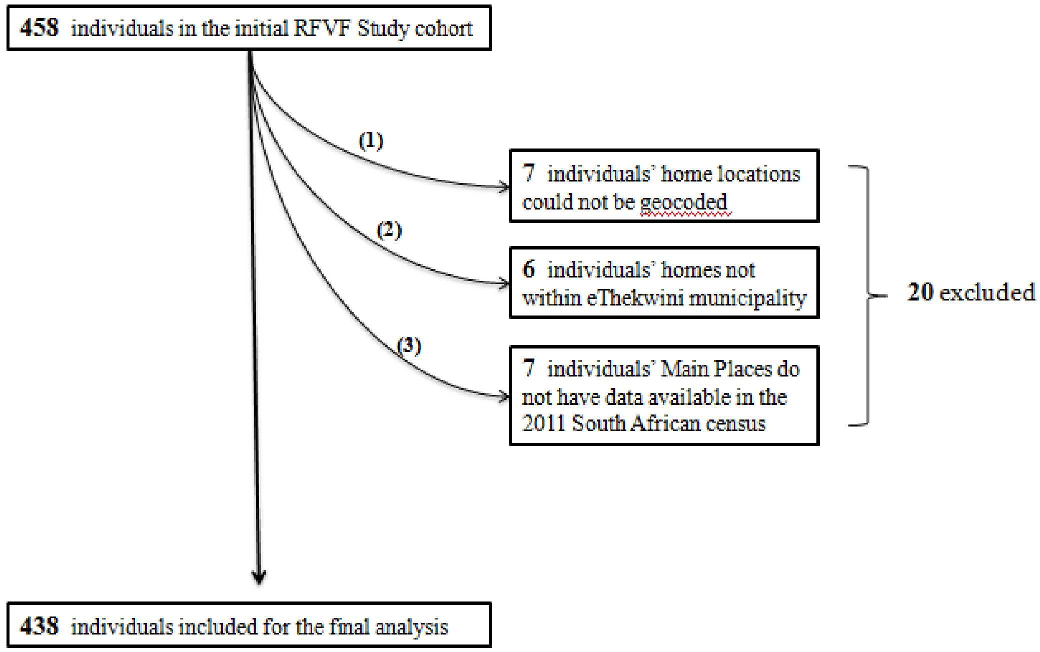

Figure 3. Shows the scheme for which individuals in the original RVFV cohort (458) were excluded from the final analysis (438). **(1)** The address information provided in the RFVF survey for 7 individuals was not sufficient to be able to locate the home address, even to the Main Place level. **(2)** In order constrain the analysis to a more concentrated study area, 6 individuals who were not located within the eThekwini municipality were excluded. **(3)** The naming scheme for several Main Places in the 2011 South Africa census tabular data did not match up to those in the GIS shapefiles. Those in the shapefiles that could not be manually linked to the tabular data included 7 individuals from the following 6 Main Places: Clifton Heights, Durban South, Illovo South, Kwantamnteng, Shongweni, and Westridge.

Figure 4. Spatial distribution of RFVF study participants in eThekwini Municipality (n=438) – Durban, South Africa

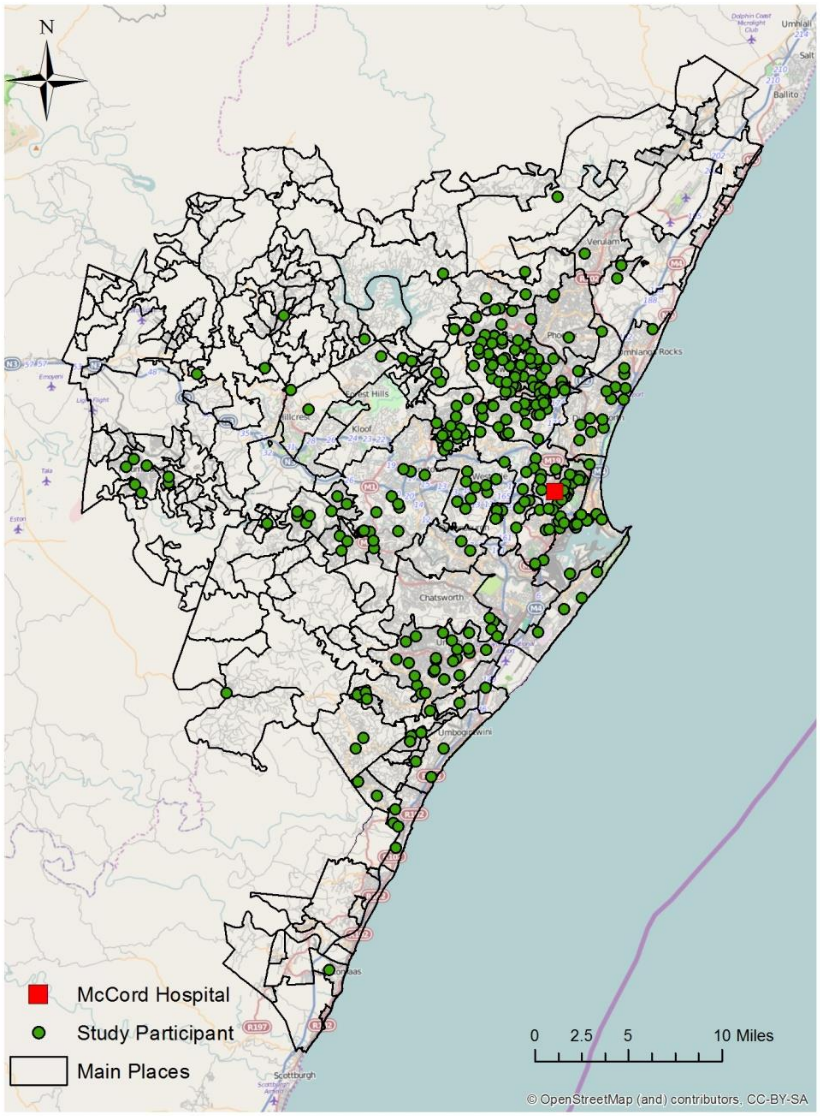

Figure 4. This map shows eThekwini municipality, the boundaries of the Main Places that make up eThekwini, and the distribution of study participants (n=438) around McCord Hospital, the study site. The map shows that the majority of study participants are concentrated in two general areas – around McCord and within the KwaMashu Main Place. Not all Main Places of eThekwini are represented in our analysis.

Figure 5. Spatial distribution of RFVF cases and controls in eThekwini municipality (n=438) – Durban, South Africa

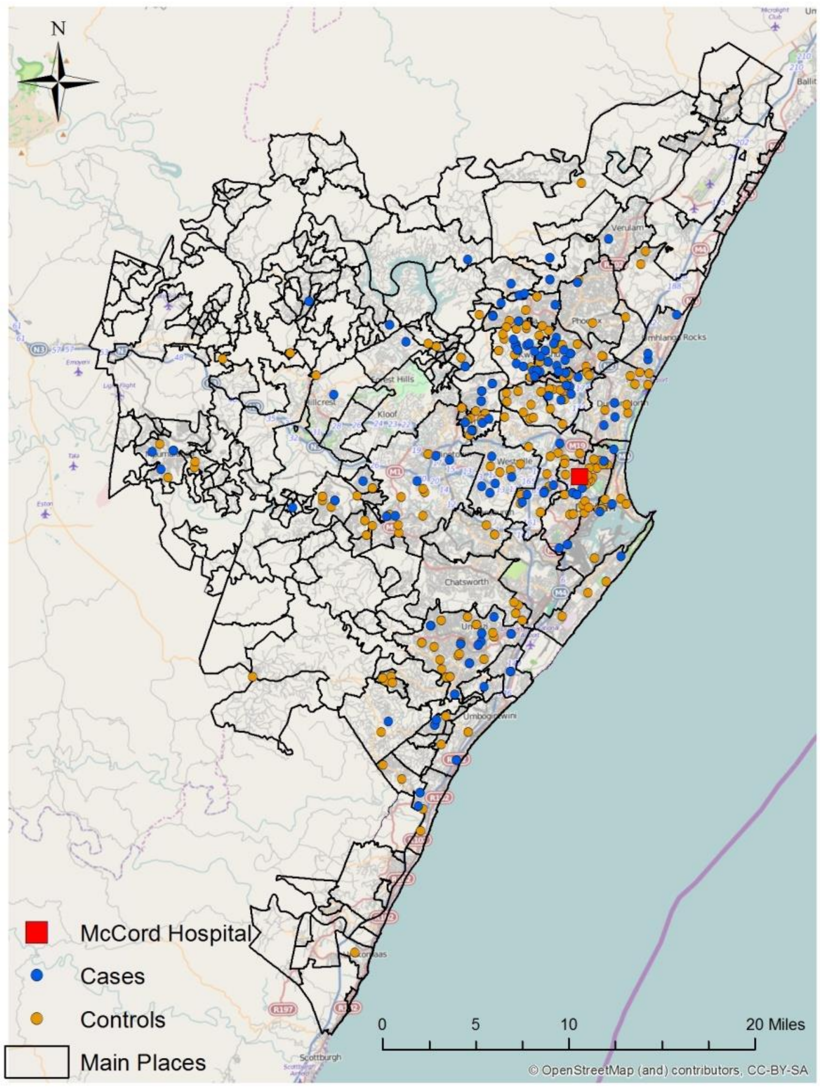

Figure 5. This map shows eThekwini municipality, the boundaries of the Main Places that make up eThekwini, and the distribution of study participants (n=438) around McCord Hospital by case/control status. The distribution of cases and controls in the current analysis suggests that there may not be significant spatial clustering of cases or controls.

Figure 6. Spatial distribution of RFVF study participants in eThekwini municipality (n=438) by neighborhood type – Durban, South Africa

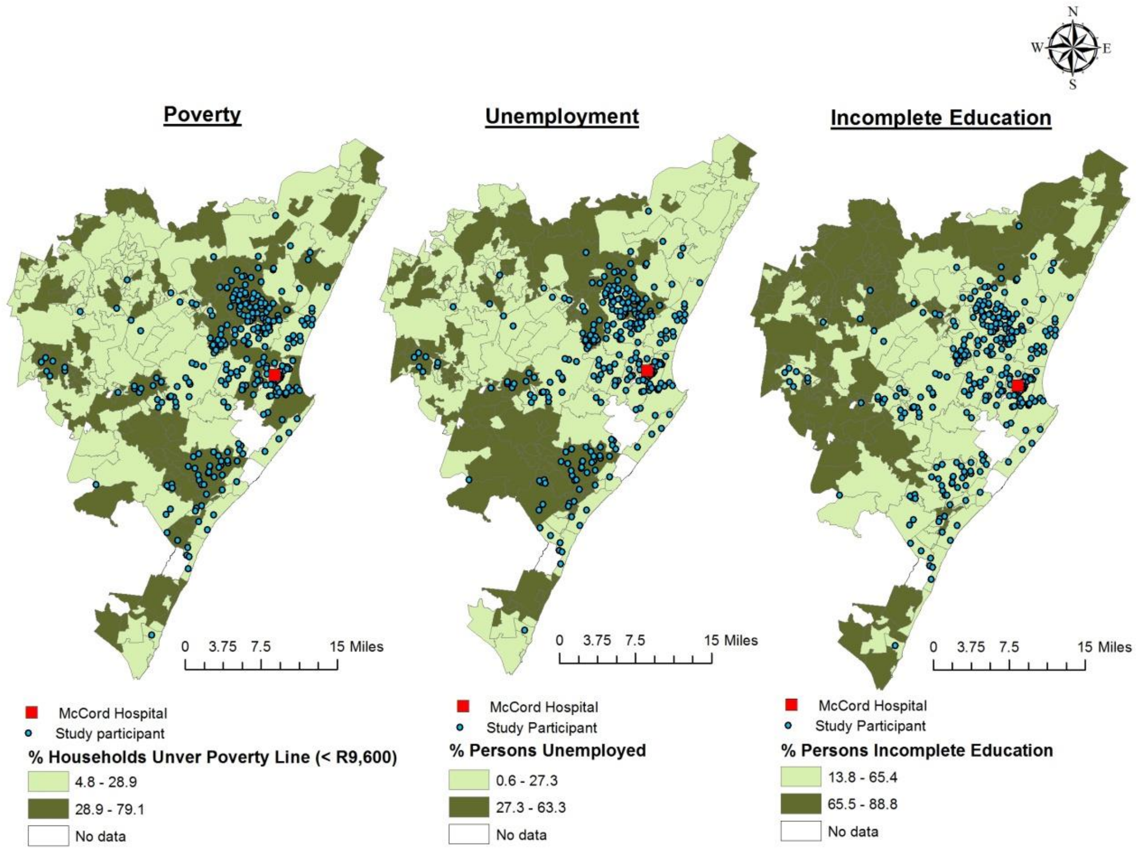

Figure 6. This map highlights the Main Places of the eThekwini municipality as high versus low poverty, unemployment, and incomplete education based on the overall municipality median value (which corresponds to the binary categorization of Main Places for the current analysis). These maps high light that while poverty, unemployment, and incomplete education are related concepts for neighborhood socioeconomic status, they may not be concordant (i.e. high poverty, high unemployment) for all Main Places. Most study participants appear to come from high poverty areas and low incomplete education areas, with roughly similar distributions in low and high unemployment areas.