The Preventive and Survival Benefits of Antiretroviral Use in a Rural South African Community

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Abstract

In this dissertation, I undertake three empirical analyses using data from the Africa Centre for Health and Population Studies, which is located in the Hlabisa subdistrict of northern KwaZulu-Natal, South Africa. In the first analysis I assess if antiretroviral therapy (ART) usage in the household is associated with a reduction in individual HIV acquisition risk. To my knowledge, this analysis is the first attempt to quantify the preventive impact of a public sector treatment program based in a rural community with poor knowledge and disclosure of HIV status, frequent migration, late marriage, and multiple partnerships. I argue in the second analysis that efforts to optimize the preventive efficacy of ART in South Africa and elsewhere will be critically dependent on the ability of the public health sector to initiate and then keep HIV-infected patients on treatment. Here, I examine the socio-demographic and structural factors that are associated with poor or imperfect adherence to antiretroviral medications, which can be obtained for free at multiple health-care centers within the study area. The third analysis continues this work by examining the diagnostic performance and cost-effectiveness of two monitoring strategies—CD4 and HIV-1 viral load count testing—to detect poor patient response to ART. My approach is based on the idea that the cost-effectiveness of a treatment monitoring strategy is a function of its predictive performance.

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Chapter 1

Introduction

In this dissertation I examine the survival and preventive benefits of antiretroviral therapy (ART) use in a rural South African community. ART can dramatically reduce the risk of mortality and improve the health outcomes of HIV-infected patients (Nakagawa et al., 2012). In recent years, research has shown that ART can also prevent the transmission of HIV from an infected individual to an uninfected, sexual partner (Baggaley et al., 2013; Anglemyer et al., 2013; Loutfy et al., 2013). Together, the survival and preventive benefits of ART have been described as a 'double-hat-trick' in the global fight against HIV/AIDS (Montaner, 2011).

South Africa has the world's highest estimated number of people (more than six million) living with HIV/AIDS (UNAIDS, 2013). In the KwaZulu-Natal province, where this study takes place, the prevalence of HIV is reported to be around 30% for 19–49 year-olds (Department of Health, 2014). Since 2004, the scale-up of ART by the South African government constitutes one of the most successful public health interventions ever undertaken in sub-Saharan Africa (UNAIDS, 2012b). Attention is now being devoted to a range of issues—notably, HIV testing and disclosure; treatment uptake, retention, adherence and resistance; risk compensation in sexual behavior; high rates of migration; and health-care capacity—that are likely to attenuate the potential of ART to substantially reduce the rate of new infections in hyperendemic communities.

In this dissertation, I undertake three analyses using data from the Africa Centre for Health and Population Studies, which is located in the Hlabisa subdistrict of northern KwaZulu-Natal. In the first analysis I assess if ART usage in the household is associated with a reduction in individual HIV acquisition risk. To my knowledge, this analysis is the first attempt to quantify the preventive impact of a public sector treatment program based in a rural community with poor knowledge and disclosure of HIV status, frequent migration,

late marriage, and multiple partnerships. I argue in the second analysis that efforts to optimize the preventive efficacy of ART in South Africa and elsewhere will be critically dependent on the ability of the public health sector to initiate and then keep HIV-infected patients on treatment. Here, I examine the socio-demographic and structural factors that are associated with poor or imperfect adherence to antiretroviral (ARV) medications, which can be obtained for free at multiple health-care centers within the study area. The third analysis continues this work by examining the diagnostic performance and cost-effectiveness of monitoring strategies to detect poor patient response to ART.

The three empirical analyses that I present in this dissertation speak to an important sociological theme. This theme concerns how the broader social context varies an individual's HIV acquisition risk, as examined in the first analysis, or adherence to ART treatment, as examined in the second and third analyses. More generally, the three analyses are confronted with the broader sociological question of how institutional processes, structural inequalities, resource allocation mechanisms, and socioeconomic status come to be embodied as individual pathology (Farmer in Diderichsen et al., 2001). In addressing this question, I suggest that it would be useful to first consider the range of causal factors hypothesized to affect a particular health outcome, and then to consider how these factors interact with one another at various levels within a hierarchical, conceptual framework. I make the argument throughout Chapter 2 that higher level factors of interest to the sociologist must operate on factors at successively lower levels within the conceptual framework before the health outcome in question can be observed. In Chapter 2, I identify and delineate three broad but distinct levels, which are the proximate determinants (Level 1), socioeconomic position (Level 2), and the societal context (Level 3). My aim in this chapter is to motivate a sociological approach to the study of health outcomes that draws heavily from this proposed model.

In Section 2.1, I turn to discussion of the social constructs and factors situated at the highest level of the proposed model. Here, I place emphasis on the broader, macro-social structures and processes that shape the everyday lives of individuals and their health. Following the work of Coleman (1994), I pay specific attention to the sociological understanding of system behavior as the product of actors or agents. This theoretical point of departure explains how high-level social actors come to define political and economic policies, shape

institutional processes, and determine the resource allocation mechanisms that result in the differential exposure and vulnerability of population groups to illness and disease. Importantly, the constructs that are situated at this macro-social level are seen to either promote or restrict an individual's health related behaviors.

In Section 2.2 I turn to a discussion of the factors associated with an individual's socioeconomic position, which represents the micro-social level of the proposed conceptual model. This level relates the quality of an individual's health to his or her position in the social system. Generally, the higher the position the better the health. Socioeconomic position is an important level in the proposed multilevel model because it marks the point at which macro-social resources enter into and affect the lives of individuals. I then turn to a review of the factors associated with socioeconomic position, and explain how these can be analyzed in relation to other levels of the proposed conceptual framework.

I introduce the proximate determinants framework in Section 2.3. I argue that this framework has been developed to identify the biological or behavioral variables through which macro- and micro-social factors must operate to influence an individual's health outcomes. The incorporation of biological variables into sociological explanations of health is admittedly not a common practice. But the reality that disease, illness, and death are also biological phenomena is inescapable; and thus whatever "factors lie upstream in the sequence of causes, at some point in the chain there must be biological processes at work" (Evans, 1994: 12). Rather than sidelining the important role of macro- and micro-social factors in the proposed conceptual model, the proximate determinants actually provide a convincing explanatory framework for how these higher level factors make their way into the human body.

I develop the proposed conceptual model in Chapter 3 by discussing the macro-social, micro-social and individual level factors that are associated with HIV-related outcomes in sub-Saharan Africa. I briefly provide a cursory outline of the viral etiology of HIV, its progression to a global pandemic, and the social determinants that make the epidemic particular to the African continent. Sub-Saharan Africa is one of the few contexts (alongside Haiti) to experience the emergence of a generalized, self-sustaining, heterosexual HIV/AIDS epidemic (De Cock et al., 2012; Caldwell and Caldwell, 1993). I argue here that the complex

epidemiology of HIV/AIDS in this context warrants the use of a conceptual framework that addressed the multilevel determinants of HIV spread and treatment adherence.

In Section 3.1.1 I review the proximate determinants of HIV: these are the behavioral and biological mechanisms through which macro- and micro-social factors must operate to affect HIV transmission and infection. I discuss the work of Boerma and Weir (2005), Lewis et al. (2007), and Bärnighausen and Tanser (2009) who have been instrumental in the development of the HIV proximate determinants framework. Much of the work in Chapter 3 is devoted to the household context, which is the micro-social level of the proposed model. The household is the site (analogous to the role of socioeconomic position in Chapter 2) where community level effects are mediated, and where social relationships define, constrain, and reproduce a range of HIV-related behaviors. The household is often considered to be the focus of sociological work, since it is a context in which decisions about sexual activity and fertility are made. I provide an extensive discussion in Section 3.1.2 of a number of household-related constructs, and devote some attention to the differences between the conjugal nuclear family system of the West and the kinship family system in Africa. In Section 3.1.3 I briefly identify and discuss four macro-social factors that are related to HIV outcomes. These are: 1) social attitudes and beliefs, 2) institutions and structures, 3) epidemiological conditions, and 4) demographic characteristics of an individual's community.

I describe the study background and data collection methods used by the Africa Centre for Health and Population Studies (Africa Centre) in Chapter 4. The Africa Centre is situated within the study area and is located in the northern KwaZulu-Natal province of South Africa. The study area is predominantly rural and consists of an urban township and informal peri-urban settlements. The Africa Centre's demographic surveillance system (ACDIS) was purposefully designed to mirror the complex demographic reality of the surrounding community. In Section 4.2 I discuss the Africa Centre's operationalization of key demographic concepts (for example, the differences between the homestead and household) which have made the surveillance data particularly flexible in terms of recording the mobility and migration of individuals in and out of the study area, among its other strengths and advantages. An important feature of the data is that it can be linked to patient records

from a public-sector HIV treatment program implemented in the 17 clinics and the local hospital within the study area.

I turn to the first empirical analysis in Chapter 5 where I examine the preventive benefits of ART at the household level. The strongest evidence for the preventive effect of ART has come from studies of HIV-serodiscordant couples—where one partner is infected and the other is not—in stable sexual relationships. In this analysis, I argue that the preventive efficacy of ART has yet to be fully quantified in communities with poor knowledge and disclosure of HIV status, frequent migration, late marriage, and multiple partnerships. These communities are common to the sub-Saharan African context. To do this, I link patients' records from a public-sector HIV treatment programme in the study area, with Africa Centre's HIV surveillance and demographic data collected between 2004 and 2012. I outline in Section 5.2 the methods used to construct the HIV prevalence and ART coverage measures for each household. I then regress the time to HIV seroconversion for 14,505 individuals, who were HIV-uninfected at baseline and individually followed up over time regarding their HIV status, on household ART coverage among coresidents of the opposite-sex, controlling for household HIV prevalence and a range of other potential confounders. I present and discuss the results in greater detail in Sections 5.3 and 5.4.

The preventive benefits of ART will be critically dependent on the ability of HIV-infected partners to take their medications up to three times per day (on a daily basis) for the remainder of their lives. In Chapter 6 I discuss how high adherence to ART is the single most important predictor of positive health outcomes and reduced mortality in HIV-infected patients. In Section 6.1 I explain and justify the use of patient viral load count—the number of HIV copies in a milliliter of blood—as a biomarker or proxy for ART adherence. I then undertake a survival and logistic regression analysis to assess the association between adherence and the socio-demographic and structural predictors. In this analysis, the socio-demographic variables capture the patient's age, sex, employment status, education level, and migration; and the structural variables specifically reflect a patient's level of interaction with the health-care setting. I then compare the magnitude of these odds ratios with a biological variable—CD4 T-cell count—to gain a better assessment of the predictors of imperfect ART adherence. Finally, in Section 6.3 I use a receiver operating

characteristics (ROC) analysis to further assess the predictive performance of the socio-demographic and structural variables.

I continue with the topic of ART adherence in the third empirical analysis of this dissertation. Briefly, the results from Chapter 6 indicate that regular interaction with the clinic setting could enable health-care providers to better monitor patient response to ART, leading in turn to the earlier detection of adherence issues and the appropriate modification of existing treatment options. However, the implementation of effective treatment monitoring strategies are often constrained by the economic realities of resource-limited settings. Although considered the gold standard, the strong diagnostic performance of viral load monitoring is offset by the logistical costs associated with centralized laboratory facilities and the HIV assay (Reynolds et al., 2009). CD4 monitoring is generally promoted as an affordable alternative to VL monitoring, but concerns have been raised about the diagnostic performance of this monitoring strategy. In this analysis, I derive a single measure that includes the cost to undertake baseline testing and the cost of incorrectly switching patients to more expensive treatment options. Again, Chapter 7 speaks to the broader sociological theme in this dissertation by considering how macro-social forces related to public health-care policy, economic conditions, resource-constraints, and institutional capacity come to affect patient response to ART.

I consider the three empirical chapters to be the substantive contribution of this dissertation. To summarize, the first analysis quantifies the preventive efficacy of ART at the household level, the second examines the socio-demographic and structural variables associated with poor adherence to ART, and the third evaluates the diagnostic performance and cost effectiveness of two monitoring strategies to detect poor adherence to ART. In each chapter I address an applied problem in the HIV treatment and care setting. As a result, I do not use the empirical analyses to evaluate, test, or confirm the multilevel framework developed in Chapter 2. In addition, the presented conceptual framework is not meant to invoke the application of multilevel statistical models in this dissertation. Rather, I consider this framework to be a backdrop to the empirical analyses presented in Chapters 5, 6, and 7. In short, I use a multilevel model of health to more generally explain how the complex set of societal, household, and individual level factors come to influence HIV-related outcomes, a task to which I now turn.

Chapter 2

A Multilevel Approach

A multilevel approach to the study of health outcomes has gained popularity in recent years (March and Susser, 2006; Raudenbush and Bryk, 2002; Diez-Roux, 2000; Susser, 1998; Coleman, 1994; Krieger, 1994; Smith, 1989). I argue in this chapter that this approach is useful for explaining how social contexts come to influence individuals and their health-related behaviors. A multilevel approach aligns strongly with a sociological understanding of health and society, which considers the individual to be influenced by multiple social systems that are arranged into successively distinct and broader levels. These levels of social influence typically include the interpersonal, household, community, and societal contexts (Scribner et al., 2010). Importantly, while individuals are considered to act and make decisions for themselves, a multilevel approach assumes that they cannot fully escape from the social reality in which they are embedded. The health-seeking behaviors of a wife, for example, are likely to be directed by the interpersonal relations with her husband, whose own behaviors are reinforced by the social expectations of a patriarchal household, which in turn are shaped by the broader social, cultural, and traditional norms of the local community. I propose to use this conceptual schema to guide and inform the empirical analyses presented in Chapters 5 and 6 of this dissertation.

In this section I present a hierarchical model of health that consists of three ordered levels, shown in Figure 2.1. At the highest level are the factors associated with the societal context (level 3). This level encompasses a set of particularly diffuse constructs, and generally refers to aspects of a social system that exert a powerful formative influence on the health outcomes of an individual or group. These macro-social factors are often described as the 'basic', 'underlying', or 'upstream' determinants of health. Below this level are the factors associated with an individual's position within the social hierarchy (level 2). In this proposed model, socioeconomic position marks the point at which the macro-social

factors (from level 3) enter into and affect the lives of individuals. It is generally believed that the higher the position in the social hierarchy, the better one's health (Cockerham, 2007; Galobardes et al., 2006; Hertzman et al., 1994). At the lowest level (Level 1) are the behavioral and biological (i.e., the proximate) determinants through which the macro- and micro-social factors must operate to affect the health of an individual.

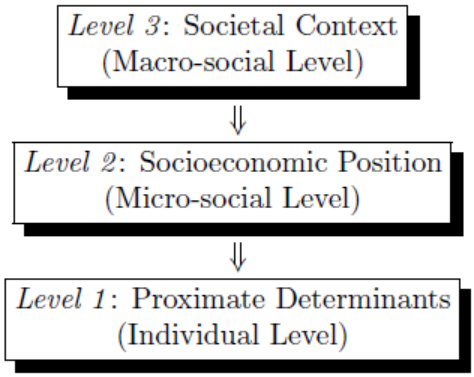

Figure 2.1: A Multilevel model of health determinants

A major challenge for sociological models of health is to explain how factors operating at the societal context come to be embodied as individual pathology. As I will discuss throughout this chapter, a multilevel approach does not consider complex societal constructs—like health-care policy, resource allocation mechanisms, or institutional racism—to directly affect an individual's health outcomes. Instead, these higher-level factors must pass through successively lower levels along the causal chain until the particular health outcome is observed. Consider the impact of economics and patriarchy, two societal level factors, on HIV transmission risk, an individual level outcome. In poor, rural communities that traditionally privilege men, a male with material resources often occupies a higher position within the social order (see Section 2.2). This socioeconomic standing will mean that he can increase the rate at which he has sexual contact with one or more partners (see Section 3.1.2). Through patriarchal beliefs and attitudes about contraception, this male may further refuse to consistently utilize condoms. Here, coital frequency, concurrency, condom use, and the concentration of HIV in the sexual partner's blood are the proximate determinants that vary the male's infection risk (see Section 3.1.1). The proposed model provides

a clear causal chain linking the broader socioeconomic context and patriarchal norms to the decisions an individual makes about his sexual behavior, which then operate through the proximate determinants to affect HIV transmission risk.

The incorporation of behavioral or biological variables into explanations of health and society is admittedly not a common practice in sociology. My use of the proximate determinants in this dissertation should not be seen as a sidelining of the important influence of sociological constructs (such as power, class, differential resource allocation, inequality, etc.) on health outcomes. Indeed, I have briefly shown in the example above how societal level factors can shape and inform an individual exposure to illness and disease. As explained, these social constructs must make their way through the lower levels of the hierarchical schema before they are embodied as individual pathology.

I do not propose here that the health outcomes of individuals can only be explained through their "actions directed toward other people and guided by their expected behaviour"—a position often referred to as methodological individualism (Hayek cited in Lukes, 1968; see also Watkins, 1952a,b, Coleman, 1994). The viability of methodological individualism as an explanatory framework has been heavily debated by sociologists since the work of Émile Durkheim, i.e., that social facts exist *sui generis*. This debate concerns whether social events or social facts exemplified by propositions concerning institutional or organizational units of analysis, can really be reduced to individual level outcomes, or to psychological or biological principles (Jepperson and Meyer, 2011; Udehn, 2002; Walsh, 1997; Elster, 1982).

I am inclined toward sociological explanation of health outcomes that are consistent with what is known about the characteristics or behaviors of more elementary units in the hierarchical framework. Here, consistency refers to the "principle that the various disciplines within the behavioral and social sciences should make themselves consistent, and consistent with what is known in the natural sciences as well" (Barkow et al. in Walsh, 1997: 123). The principle of consistency respects the demarcation of distinct levels of analyses by academic discipline: for example, the sociologist would seek to investigate the impact of systemic behavior on population health differentials, whereas a psychologist would be prompted to examine the psychological motives that increase or decrease exposure to health risks; a biologist would be inclined to examine the set neural, hormonal, evolutionary and genetic factors that determine individual susceptibility to health pathology. Thus,

vertical integration occurs in a multilevel explanatory system when the levels of analysis are consistent with one another.

In health research, biological explanations may satisfactorily identify the genetic or immunological mechanisms that result in the succumbing of an individual to a sexually transmitted infection (to use an example of a health outcome). But this explanation may not be sufficient to explain a difference in prevalence between two population groups, unless the biologist is able to demonstrate some genetic or immunological feature that differentiates population A from population B in terms of infection susceptibility. The sociologist may better account for this difference in prevalence by identifying some macro-social factor, say, a particular institutional arrangement that is highly successful in informing and educating the populace about safe sex practices, and supplying and distributing the necessary health care services and resources to achieve this end. This hypothetical scenario could be construed as an example of vertical integration because the explanation for the institutional difference between the two populations is consistent with the biological explanation for how sexual infections are transmitted, i.e., increased condom use in population A or B (but not both, and holding all else equal) would reduce the risk of exposure to infected blood or semen during the course of a single sexual episode. Explanations which restrict cultural or experiential meaning to the social domain only, and which cannot link these insights to lower level phenomenon may not be as effective in accounting for the observed difference in disease prevalence in our hypothetical scenario.

2.1 Societal context

Those who work from a sociology of health perspective are concerned with explaining how broader, macro-social structures, processes and institutions shape the everyday lives of individuals and their health. From this perspective, attention is drawn to the political, economic, and cultural contexts of population health; the social system which configures, stratifies and reproduces health dynamics; and the resource allocation mechanisms that result in the differential exposure and vulnerability of population groups to disease and illness. The inclusion of societal context as a higher-order level can be motivated by the observation that systemic or institutional factors often constrain or regulate the decisions individuals make about their health. Referring to fertility outcomes in the developing

context, Herb Smith (1989: 172) alludes to the importance of macro-social factors with the following example.

> Patriarchy is a social institution subsuming large numbers of women within families, families within kin groups, and kin groups within communes or villages. The subordination of youth to their elders and of women to men is not a feature of particular households, families, or kin groups, but of the larger social structure. Individual variation (deviance) is of little account when arrayed against the larger forces militating for conformity to essential behaviors, including fertility. When change comes, it comes not through the collective exercise of individual choice, but through the collapse of a larger system that had heretofore constrained all choices of behavior open to individuals.

The fertility example above illustrates how the decisions individuals make with regard to their reproductivity come to be determined by multiple social influences. From a sociological perspective, these influences emerge from the behaviors of social actors operating at the societal level. Here, the meaning of the social actor differs from our understanding of the individual as a person. The social actor is an authorized agent who chooses interests and actively manages the rules of the social environment (Meyer, 2010: 3). Rather than being embedded objects within the institutional structure, the social actor is a competent, rational decision maker and strategist.

A good example of this kind of social actor is in the sphere of governance, which refers to the means by which a society organizes itself and implements decisions. The most well known social actor in this context is a political party, a coalition, or a social movement that acts to realize a set of interests that may substantially shape or reconfigure the social system. In some historical examples, the rise of a cultural or political group to power has resulted in the total transformation of the social order, including the resource allocation mechanisms that affect health (Gilson and McIntyre, 2001).

Social actors can develop and implement macroeconomic policies, which determine the formal allocation of resources at the national and local level. This sphere of social influence typically involves labor market policies designed by social actors to regulate or provide incentives for individuals, organizations or corporations. Macroeconomic policies may help

to assist disadvantaged groups, or they may privilege the needs of one social group over another.

Social and public policies are implemented by political actors, often positioned in the sphere of governance, and provide the legal basis for the distribution of social goods and services. The intentions of such policies can affect a range of social factors from labor practices to social welfare, housing and land distribution, education, and basic municipality services. Closely related to this sphere of influence are cultural and social values, which may involve the degree to which a set of actors frame health as a priority, the extent to which collective resources are directed toward public health programs and services, and willingness of a society to assume responsibility for the distribution of social resources.

In the discussion above, I considered how an individual's health risks and opportunities are shaped, informed, and reproduced by a set of social actors, which could be global or international actors (e.g., the World Health Organization), national actors (a ruling political party) or local actors (a husband). Social actors achieve these ends by exerting patterned effects on the actions of individuals without requiring repeated and authoritative interventions to achieve these regularities (Clemens and Cook, 1999). In this way, social actors provide scripts and schemas for a range of social behaviors, and these behaviors are in turn reinforced through numerous socialization processes. Some of these processes may involve constraints on social action (lack of political will to provide basic health care services at the national level), the shaping of institutional interactions (government policies which restrict the ability of medical institutions to dispense medications), or control over the access to resources (delays in the comprehensive roll out of life saving treatments).[1] In many respects, social actors are the "central engine" powering the types of macro-level factors that affect health (Diderichsen et al., 2001: 16). The macro-social factors listed above implicitly point to the key sociological concepts of power, prestige, status, and hierarchy, which emerge more explicitly in the micro-social level (socioeconomic position) of the proposed conceptual model discussed below.

[1] The examples in parenthesis are based on the South African government's decision to delay the roll out of life saving medications to HIV-infected individuals between the years 2000–2004 (see Forsyth et al., 2008; Butler, 2005).

2.2 Socioeconomic position

Factors associated with socioeconomic position comprise the second level of the proposed conceptual model. Socioeconomic position refers to "the social and economic factors that influence which positions individuals or groups will hold within the structure of society" (Galobardes et al., 2006). Socioeconomic position is an important level in this proposed model because it is generally believed that a person's health is linked to the position he or she occupies within the social system (Cockerham, 2007; Galobardes et al., 2006; Hertzman et al., 1994).

According to Graham (2004: 107), it is socioeconomic position that marks the point in the model where societal level resources "enter and affect the lives of individuals." An individual's position in the social hierarchy can determine the degree of access to and control over resources, which in turn can be used to minimize or avoid risks of disease or illness. Such resources may include power, wealth, prestige, social capital and social support. Because resources are unevenly distributed throughout society, certain groups or individuals ultimately acquire a greater or lesser share of the stock of private or public resources. The capacity to access resources is strongly associated with the amount of wealth, status and power one has in society. Typically, this is indicated by the construct social class, which is loosely defined here as a category or group of people arranged in a hierarchical pattern from top to bottom (Cockerham, 2007). Those at the top will have better access to safer neighborhoods, sources of wholesome foods, health knowledge, behavioral intervention strategies, and medical care—resources which improve an individual's health opportunities. The distribution of such resources in the social hierarchy is uneven, and it is precisely this reality which produces and maintains population health heterogeneity.

The relationship between socioeconomic position and health can be more formally outlined as follows:

- Society is hierarchically stratified. This stratification leads to the formation of groups, the members of which share a common position and shared 'life chances' (Galobardes et al., 2006).
- Because of the hierarchical configuration of society, social groups are arranged relative to other groups at the top or bottom of the hierarchy.

- Socioeconomic positions are therefore inherently unequal, and a person's socioeconomic position may leave him or her either advantaged or disadvantaged in relation to members of other social groups.
- Because of the hierarchical stratification of society, the resources that enter into the social system are unequally distributed. As a result, structural and institutional factors begin to reinforce and reproduce the inequalities associated with one's socioeconomic position. This "determines access to resources at every point in the casual chain: societal, environmental, behavioral, and disease related" (Graham, 2004: 112).

The focus on the key sociological terms of hierarchy, inequality, resources allocation, and status requires us to think of the determinants of health in two notionally distinct, but interconnected ways. A first formulation of the term refers to the social causes of ill-health. The social causes of ill-health, which Graham (2004) calls *health determinants*, describe the vector of social factors that promote and undermine the health of populations and individuals. The social factors that relate to the social position of an individual (for example, educational qualifications, occupational mobility) and the socioeconomic context in which an individual is embedded (for example, high living standards and life expectancy) are considered to be important health determinants. The second formulation refers to the social causes of disparities in health, which Graham calls *health inequality determinants*. In the context of this paper, the distinction between health determinants and health inequality determinants is important because the latter formulation refers to the "social processes underlying the unequal distribution of these factors between groups occupying unequal positions in society" (Graham, 2004: 102). Thus, while many industrialized nations have recently witnessed improvements in the factors associated with better health, these improvements have done little to significantly reduce the poor health outcomes of groups characterized by some social disadvantage (i.e., groups that are poor, non-white, female, unemployed or working class). From a public health and policy perspective, initiatives devoted to addressing *health inequality determinants* may require different programmatic features relative to the management of *health determinants*.

While the importance of socioeconomic position as a determinant of health has been stated, the more difficult question arises as to how to define its measurement and how it can be analyzed in relation to other determinants in a multilevel setting. This task is

complicated by some obvious difficulties. First, the construct of socioeconomic position is broad and defies a concise definition. Second, socioeconomic position is a latent variable that cannot be directly measured (Oakes, 2011). Third, socioeconomic position differs according to the place one holds in the social hierarchy. A measure of social position will have to be sensitive to the social, economic, cultural and demographic factors of a person's life situation, a complexity which is empirically difficult to capture. Oakes and Rossi (2003) and Oakes (2011) devote greater attention to the available composite or proxy measures that have been developed to measure socioeconomic position, six of which I review below.

Social Class: Max Weber defines class as the typical probability of 1) procuring goods, 2) gaining a position in life, and 3) finding inner satisfactions, "a probability which derives from the relative control over goods and skills and from income-producing uses within a given economic order" (Weber, 1978: 302). It is through class structures that health inequalities are generated and maintained. Social class contours stratification which allocates power and wealth to groups and individuals. One of the more important aspects of class in this context is the intergenerational transfer of economic position from parents to their children. In this way parental incomes have a strong impact on child health that is not due to genetic inheritance or the health status of parents (Bowles and Gintis, 2002; Warren and Hauser, 1997: 17). Parental income and wealth are therefore strong predictors of likely economic status of the next generation. Such intergenerational transmission is further consolidated as the advantages or disadvantages of a particular class membership position accumulate over time.

Income: One way to capture a person's position within the social hierarchy is through income. Income is an indicator of an individual's material possessions, which is converted to expenditure on improved health enhancing environments, behaviors, and services. For example, income can be used to purchase more nutritious foods, better housing and safer neighborhoods, easier access to health care and prevention, and so on (Galobardes et al., 2006). Since money is related to status and prestige, an improved social standing may result intrinsically in improved self esteem and self worth, which in turn positively affects health outcomes. In this way, psycho-social factors may provide a buffer to environmental risks and exposures which damage health. It should be recognized, however, that income and income inequality are not the same constructs. Lynch et al. (2004) argue that despite

discussion of fundamental causes, there is little that has been said about the fundamental mechanisms that link social disadvantage to different sorts of health outcomes. They stress the importance of recognizing that the determinants of health differ at the population and individual levels. A distinction must be made between income inequality which is a characteristic of the social system, and income, which is a characteristic of the individual. The former may be determined by broad macro-social contexts related to history, politics and economics. The latter, on the other hand, is determined by a person's cognitive abilities, education, skills and aptitude for certain tasks. A multilevel approach suggests that the investigator be attentive to the differences between macro-level determinants and individual level outcomes. Such a distinction will help to specifically address the role of income inequality as a social determinant of health.

Race and Gender: The term race is a socio-political-cultural construct that is "deeply unstable and internally contradictory" (Omi and Winant, 2011: 367). Nevertheless, race is often considered to be an important construct because it has shaped, and continues to shape, the social system in which we live. Gender, like race, is a social construct which is also a fundamental basis for discrimination, limiting access to power, prestige and resources for the majority of women. Race and gender have been the principal components of social formation and stratification, with groups being ranked (often on the basis of sex, skin color or other phenotype characteristics) in such a way so as to privilege some and disadvantage others. Societal determinants shape definitions of race and gender which put into play institutional policies and practices which in turn affect socioeconomic position. There is both an institutional and individual dimension to racism and sexism, and it is the former that is of importance as a social determinant of health. The implementation of discriminating policies, systematic inequality and differential access to health care are broad cases of institutional racism and sexism that may affect how health care resources are accessed and utilized (Kunitz and Pesis-Katz, 2005). From a multilevel context, understanding racism and sexism as an institutional rather than a specifically individual construct may help us to understand differences in health status between groups of color and sex (Williams, 1997; Karlesen and Nazroo, 2006).

Education: This is an indicator that measures early life socioeconomic position; it also operates in a number of ways to influence health outcomes at the group and individual

level. Education is one of the primary ways in which an early adult transitions from their parent's received socioeconomic position to their own socioeconomic position. Parental educational attainment has a direct relationship with a child's educational opportunities, and a father's education and social class have been shown to affect a child's health status at birth (Case et al., 2005). The attainment of cognitive, intellectual skills and abilities in early childhood may predispose individuals at a later stage in the life course to be more receptive to health education messages and engage in health promoting behaviors. Advanced educational status may also result in better living standards and employment, which translate into better health outcomes. While children from higher income families typically have higher educational attainment, the experience of poorer childhood health and lower investments in human capital are associated with lower educational attainment (Case et al., 2005; Warren and Hauser, 1997). Disadvantages associated with ill health may limit access to subsequent educational resources, and further predispose groups with limited educational opportunities to the onset of adult diseases and complications over time.

Occupation: This is an indicator of socioeconomic position, and is related to health outcomes in a number of ways. Marmot et al.'s (1991) classic study of British civil servants showed a strong association between occupation and mortality. The authors report that those lower in the income grade hierarchy were more likely to report financial and housing difficulties. One of the key mechanism linking occupation to health is income. As discussed earlier, income can determine the access to and accumulation of material resources. These resources can be used by an individual to reduce his or her exposure to disease, toxicity, and illness. Occupational hierarchy can also expose workers to a specific pattern of health risks (Diderichsen et al., 2001). Lower class groups or individuals typically work in conditions which expose them to higher levels of toxicity and disability (Case et al., 2005). For example, manual workers (compared to non-manual workers) undertake strenuous tasks that involve repetitive strain, physical labor, alongside continuous exposure due to often harsh weather conditions—factors which increase the risk of mortality. Workers with lower control over their job and higher work load are also at greater risk of disease, are less likely to exercise and maintain a balanced diet, and are likely to have lower educational achievement (Marmot et al., 1991). Chronic health conditions in childhood can also significantly affect opportunities for employment in adulthood (Case et al., 2005).

These proxy measures help to illustrate the importance of socioeconomic position as a health inequality determinant. Due to the conditioning effects of socioeconomic position, subgroups and individuals are likely to demonstrate behaviors that increase their exposure to particular health risks; and individuals higher up the social hierarchy will tend to be less afflicted by illness. As I have mentioned, the spotlight on health disparities and inequalities introduces us to the idea that groups or individuals who have better access to social goods, capital and resources are able to enact a range of protective measures that secure their health prospects. It is in this respect that Link and Phelan (1995: 81) stress the relevance of social conditions as the "fundamental causes of disease". They argue the need to shift our attention away from the belief systems of Western culture which stress the capacity of individuals to control their personal fate, a belief system which has orientated the explanatory models of health outcomes to focus on only on proximate risk factors or individualized care (of the ill or the sick). Such a viewpoint counters the prevailing cultural and programmatic treatment of social conditions and health, and pose the question of what social factors put "people at risk of risks?" (Link and Phelan, 1995: 85).

2.3 Proximate determinants

In the preceding sections I presented the macro- and micro-social levels of a hierarchical model of health. I argued that socioeconomic position assumes a critical position in the multilevel model because it is the point at which societal level factors enter into the lives of individuals. These macro- or micro-social factors, however, do not directly cause poor health, illness or disease. From the perspective of this conceptual framework , the societal and socioeconomic variables must operate through a set of intermediary variables in order to influence individual health outcomes. These intermediary variables are called the proximate determinants of health.

The proximate determinants framework has been developed and used most extensively in the field of demography. In this context, demographers have been mainly concerned with explaining how the macro-level processes of fertility, morbidity and mortality differ across social groups. Davis and Blake (1956) first outlined an analytic framework for studying differences in population fertility due to the effects of social structure. Comparative analyses

typically show profound variation in fertility levels despite the biological, and hence universal, process of human conception and birth. As conceived by Davis and Blake, an analytic framework must classify the intermediary variables through which social factors operate to affect fertility levels. Three temporally ordered steps in the reproductive process, which are generalizable to human culture, can be identified as: 1) intercourse, 2) conception and, 3) gestation and parturition. The eleven intermediate variables are subsets of these three stages in the reproductive process.

There are six factors that affect exposure to *intercourse* (defined as the formation and dissolution of unions in the reproductive period, or exposure to intercourse within unions): 1) The age of entry into sexual union; 2) permanent celibacy which is the proportion of women never entering sexual union; 3) the amount of reproductive period spent after or between unions (when unions are broken by divorce, separation, or desertion, or by broken by the death of husband); 4) voluntary abstinence; 5) involuntary abstinence; and 6) coital frequency. The factors affecting exposure to *conception* involve 7) fecundity or infecundity as affected by involuntary causes; 8) the use or non-use of contraception (by mechanical, chemical means, or other means; and 9) fecundity or infecundity as affected by voluntary causes such as sterilization. The factors affecting *gestation and parturition* include 10) fetal mortality from involuntary causes; and 11) fetal mortality from voluntary causes.

Without specifically stating how cultural factors operate through these eleven intermediary variables, attempts to explain the relevance of cultural factors on fertility are typically "inconclusive" or "confused" (Davis and Blake, 1956: 213). By definition, these intermediary variables are not culturally specific, must exist in every society (through biological necessity), and all eleven intermediary variables must be included in a fertility analysis. The effects of the intermediary variables on fertility are either positive or negative. For example, the practice of celibacy or contraception would naturally suppress fertility (holding the remaining intermediary variables constant), whereas increased coital frequency would have an enhancing effect. If, for reasons relating to certain characteristics of social organization, a subset of the intermediary variables are ruled out, then the remaining subset must account for or explain the pattern of fertility within that social context. Due to the particularities of social contexts, different population groups may have varying combinations of the intermediary determinants, as in the case where industrialized societies, for example,

tend to have higher values on contraception, or delayed age at marriage, when compared to societies from the developing context.

To demonstrate their framework, Davis and Blake (1956) refer to the historical case of Ireland, and decompose the role of cultural-economic factors on the intermediary variables of fertility. The authors claim that the cultural determinants of inheritance along with partrilocal factors contributed to later marriage among the Irish, which resulted in decreased levels of fertility. They argue that the causal relationship between the cultural-economic characteristics of Ireland and fertility patterns can only be properly understood by identifying and classifying the intermediary variables through which the underlying determinants operate. The work of Davis and Blake is cited here because of the conceptual attempt to explain the pathways through which macro-social processes influence biological outcomes.

Bongaarts (1978) and Bongaarts and Potter (1983) replaced the term intermediary variables with the proximate determinants, and further developed the fertility framework of Davis and Blake (1956). The proximate determinants directly influence fertility: a change in the value of one proximate determinant (holding the remaining determinants constant), is associated with an increase or decrease in a fertility outcome. Fertility variations or changes at the population level should thus theoretically be traced to a change in one or more of the proximate determinants. While socioeconomic factors may be weakly correlated with fertility levels, they may strongly influence the proximate fertility determinants. Each proximate determinant has a separate influence, indicating the possible pathways through which socioeconomic factors can influence fertility outcomes. Bongaarts (1978) list eight determinants of fertility relating to the factors that affect *exposure* 1) proportion married; *marital fertility control factors* 2) contraception and 3) induced abortion; and *natural fertility factors*, which are 4) lactational infecundability, 5) frequency of intercourse, 6) sterility, 7) spontaneous intrauterine mortality, and 8) duration of the fertile period.

Bongaarts (1993) paper is a working example of a proximate determinants framework in action, which is a methodical attempt to parse out the effects of socioeconomic development versus family planning interventions on fertility levels in developing contexts. Bongaarts is in effect grappling with the question of how to account for the role of competing macro-social processes (or institutional effects) on fertility rates and outcomes. To address this question, Bongaarts specifies the outcome variable as a measure of reproductive performance,

or fertility. The physiological process of birth is defined as a function of three proximate determinants: 1) *supply of births* measured as natural fertility, 2) *demand for births* measured as wanted fertility and, 3) *degree of preference implementation*, scaled from 0 to 1, which measures the decision making process in which couples weight the cost of fertility regulation against unwanted childbearing. The macro-social processes of socioeconomic development and family planning are mediated by the behavioral and biological variables of supply, demand and preference implementation. Bongaarts tests his model by regressing the three proximate determinants on socioeconomic development and program effort. The results show that the "development index has a highly significant impact on wanted fertility and the programme effort score is a highly significant determinant of the index of preference implementation" (Bongaarts, 1993: 452). Using this framework, Bongaarts (1993: 453) argues that past studies "of the determinants of fertility have been hampered by the absence of a convenient analytical framework for quantifying the relationships between successive layers of factors that link fertility to its basic determinants."

Bongaarts and Potter's identification and selection of the proximate determinants of fertility has not gone without critique. (A review of this critique is beyond the scope of this paper, see Stover (1998) for a more detailed discussion.) My aim has been to flesh out the potential mechanisms by which social things make their way into the human body. As discussed above, the proximate determinants framework provides a useful methodological means for getting at this question. This framework can be applied to health outcomes other than fertility, as will be discussed in more detail in Section 3.1.1. A proximate determinants framework may further help the analyst to identify and order the various competing risks that interact to affect the health and well-being of individuals. This conceptual proposition need not necessarily be construed as challenging the contribution of important sociological precepts (power, class, differential resource allocation, inequality, etc.) with respect to the study of health outcomes. The biological and behavioral factors, which are situated at the individual level, are the components through which the influences of these deeper social forces are realized.

A note on the application of multilevel models in statistics

In this chapter I have discussed how a multilevel approach, along with the proximate determinants framework, can be used to outline the causal mechanisms by which societal-level factors influence individual health outcomes. I find it necessary at this stage to make a distinction between the multilevel framework proposed in this dissertation and the use of multilevel models in the statistical analysis of health data. Essentially, my aim is to present a conceptual framework that explains how societal level factors are manifested as individual pathology. Here, I make a loose appeal to notions of causality by delineating the series of levels through which societal level factors must operate in order to influence the health of an individual. It is in this context that I make use of the term 'multilevel'. Multilevel statistical models, on the other hand, seem to be primarily concerned with the technical problems related to the grouping of individual properties within hierarchically ordered levels. In this context, the assumptions of traditional linear models are violated because of the untenable assumption of independent or uncorrelated residuals. Multilevel statistical models offer a way to account for the hierarchical nature of the data so that so that the appropriate estimates and standard errors can be produced.

In this dissertation I consider the question of how social things make their way into the human body to be quite different from the technical issues raised by the hierarchical structure of (health) data. The former relates to an epistemological approach that draws more broadly on the ideas of causality and the principle of vertical integration. Arguably, the latter appears to be a statistical response to the empirical challenges inherent in the spatial and temporal ordering of our social reality. I am concerned more with the first than the second theme, and as a result I do not attempt to test the proposed conceptual framework through the statistical application of multilevel models in this dissertation. Indeed, I do not consider the proposed multilevel model presented in this chapter to be the definitive contribution of the dissertation. Once developed over the course of Chapter 3, I consider the proposed conceptual framework to remain 'on-call' or in the 'background' as I turn to the essence of this work, which is contained in the three empirical chapters. Thus, instead of validating a theoretical or statistical approach, each empirical chapter in this dissertation addresses an applied problem in the real-world context of HIV treatment and care—it is in this area that I endeavor to make the substantive contribution.

Chapter 3

The Epidemiology of HIV/AIDS

HIV/AIDS can be described as one of history's worst pandemics, resulting in more than 60 million infections and 30 million deaths (De Cock et al., 2011). Globally, HIV continues to spread unabated and with no end in sight. By the end of 2010, the total estimated number of adults and children living with HIV was 34 million (31.6–35.2 million), another 2.7 million (2.4–2.9 million) were estimated to be newly infected with HIV, and 1.8 million (1.6–1.9 million) were estimated to have died of AIDS (UNAIDS, 2011).[1] The goal to have more than 5 million people on treatment constitutes one of the biggest public health interventions thus far witnessed (UNAIDS, 2010). By 2010, however, only 20% of sub-Saharan Africa was estimated to have ART coverage (UNAIDS, 2011).

AIDS (Auto-Immune Deficiency Syndrome) is caused by the retrovirus HIV (Human Immunodeficiency Virus). Retroviruses differ from other viruses because they can transcribe DNA (deoxyribonucleic acid) from a viral RNA (ribonucleic acid) template, a process that is reverse to the usual flow of genetic information (Montano and Williamson, 2002).[2] At the initial stage, HIV attaches, encodes, fuses, and then penetrates the cellular membrane of a host cell. Once inside the nucleus of a host cell, the HIV pathogen utilizes a reverse transcriptase enzyme to create a DNA copy of the viral genome, which it then synthesizes with the host DNA strand. The now combined DNA strand is passed over into the new cell and finally released as an independent cell—a process that ensures the replication of

[1] Uncertainty ranges of point estimates reported in parenthesis.

[2] Viruses are non-living particles that have two parts: an outer capsid composed of protein subunits, and an inner core of nucleic acid, either RNA or DNA, but not both. The capsid is surrounded by an outer membranous envelope, which contains viral glycoprotein spikes used to interact with the membrane of the host cell. Having penetrated the membrane, a retrovirus relies on the host's enzymes to function; ribosome's (portions of the cell responsible for metabolism) transfer RNA and adriosine triphoshate for its own production. Retroviruses—HIV belongs to a sub-group called lentiviruses—replicate by taking over the metabolic machinery of the cell it has infiltrated.

the viral genome for a lifetime. (HIV replication can also take place in non-dividing cells.) Because reverse transcriptase does not have a proofreading function, errors are allowed to go uncorrected during the viral life cycle. These mutations, which respond rapidly to evolutionary pressures, result in advanced resistance to antiretorviral (ARV) development and further forestall the discovery of an AIDS vaccine or 'cure' (Kuritzkes, 2011).

Once integrated into the DNA replication process, HIV targets specific CD4 T-lymphocyte cells, also known as helper T-cells. T-cells help to stimulate the production antibodies that recognize and destroy foreign pathogens. A host's immune system is compromised by the twin burden of increasing viral load (due to replication) and a decrease in CD4 cells; at a critical stage, the infected person is neither able to contain nor eliminate a broadside of opportunistic (viral, bacterial, fungal and parasitic) infections. There are three phases following HIV infection: the period of primary infection; an asymptomatic period; and finally, overt AIDS. HIV can take 1 year to more than 20 years to progress to full blown AIDS; the median time to onset is 10 years, and in sub-Saharan Africa the average duration is only 8.5 years. Variability in the progression to AIDS depends upon the susceptibility of the individual, HIV virulence, immune response, and other endogenous and exogenous co-factors. Progression and measurement of immunodeficiency in an individual is determined by the number and percentage of CD4 and CD8 T-lymphocytes in the blood. Individuals with counts less than $50/\text{mm}^3$ have a 50% annual mortality rate, while individuals with counts of less than $200/\text{mm}^3$ have mortality rates of 10% to 15% per year (Zijenah and Katzenstein, 2002).

HIV-1 and HIV-2 are the two types of retroviruses known to cause AIDS. HIV-1 contains a further 14 sub-types (A–K, M, N and O) (see Hemelaar et al., 2006 for a more detailed description of the geographical origins of each of these sub-types). HIV-1 is the predominant cause of the AIDS epidemic in sub-Saharan Africa, and is thought to have originated from three cross species transmission events to produce three distinct sub-groups (M, N and O) (Diop et al., 2002). The oldest case of HIV-1 was traced back to a man living in Leopoldville, Belgium Congo (now the Democratic Republic of Congo) in 1959 (a retrospective diagnoses of his blood specimen was undertaken). This sample was shown to be close in sequence to HIV-1, and thought to enter into the human population in the 1940s (Montano and Williamson, 2002). In 1985, a second AIDS-causing virus, HIV-2, was discovered; at the

time cases were reported in most west African countries. While sharing many virologic and biological features of HIV-1, studies have shown HIV-2 to be limited in its spread, to have lower rates of sexual and perinatal transmission, slower progression to AIDS, and a protective effect against subsequent HIV-1 infection (Kanki et al., 2002). The spread of HIV-1 and HIV-2 went unnoticed throughout Africa in the 1970s.

In the early 1980s homosexual men in the United States began to clinically present with a set of symptoms that have since became known as AIDS. By 1983 it was understood that sexually transmitted infections and blood transfusions were the major pathways of this yet unidentified AIDS agent (De Cock et al., 2012). In the United States, early risk groups were identified as men who have sex with men (MSM), intravenous drug users, blood transfusion recipients and hemophiliacs. In 1983 French scientists isolated HIV-1, and the following year American scientists presented evidence that HIV was the cause of AIDS.[3] During this period, little was known of HIV/AIDS outside of the United States. Subsequently, cases were reported in Haiti, then in Europe and over the next decade the epicenter of the epidemic moved from California to a full-scale global pandemic. In the United States, western Europe, Australia and New Zealand, and parts of Latin America, HIV infection was predominant in men who have sex with men, whereas intravenous drug use characterized transmission routes in southern Europe, parts of south and south-east Asia, and countries in the former Soviet Union (De Cock et al., 2012).

By the mid-1990s more than 20 million people were estimated to be living with HIV/AIDS. In 2001 an estimated 20.3 million (20.9–24.2 million) adults and children were living with HIV, 2.2 million (1.9–2.4 million) became infected, and 1.4 million (1.2–1.6 million) people were estimated to have died of AIDS in sub-Saharan Africa alone (UNAIDS, 2010). That year, sub-Saharan Africa accounted for three-quarters of the world's AIDS deaths. In this context, AIDS was responsible for one in five deaths, twice as many as the second leading cause of death (Piot and Bartos, 2002). UNAIDS (2011) figures put the total number of new HIV infections in sub-Saharan Africa for 2010 at 1.9 million (1.7 million–2.1 million), with the total number infected estimated at 22.9 million (21.6–24.1 million). Despite declines in the total number of people being infected with (and dying from) AIDS, the sub-Saharan

[3] The group of scientists under the leadership of Robert Gallo initially called HIV human T-lymphotropic virus type III (HTLV-III).

region remains the most heavily affected by HIV.[4] With only 12% of the world's population, 68% of all people living with HIV reside in sub-Saharan Africa, a region which also accounted for 70% of new HIV infections in 2010 (UNAIDS, 2011). Substantial geographic variation in HIV prevalence exists in this region, with Swaziland and South Africa estimated at 25.9% (with a 95% CI of 24.9% to 27.0%) and 17.8% (17.2% to 18.3%) respectively, and Senegal at 0.9% (0.7% to 1.0%) for adults aged 15–49 years in 2009 (Lewis, 2011).

In sub-Saharan Africa, HIV is predominantly spread through heterosexual intercourse (horizontal transmission) (Caldwell and Caldwell, 1996, 1993).[5] There are three biological factors that have been identified to determine the heterosexual transmission of HIV. These are 1) the exposure of susceptible to infected persons, 2) the efficiency of transmission per contact, and 3) the duration of infectivity (Boerma and Weir, 2005).

The probability of HIV transmission for one sexual act between a heterosexual couple is thought to be around 0.001 (Cohen, 2012). Transmission efficiency is known to be enhanced in the presence of sexually transmitted diseases (STDs), high numbers of lifetime sexual partners, and intercourse with sex workers (Cohen, 2012; Tanser et al., 2011; Shahmanesh et al., 2008; Hargreaves et al., 2008; Lewis et al., 2007; De Walque, 2006). Transmission events in 10–30% of couples typically involve a third partner (Wawer et al., 2005), and only a minority of new infections occur between couples in a stable relationship (Gray et al., 2011). Viral load—defined as the number of copies in a milliliter (copies/ml) of blood—is becoming more widely recognized as a major determinant of the infectivity level of an HIV positive person (Smith et al., 2011). In one of the earliest and most widely cited studies, Fideli et al. (2001) showed that the viral load of the index case was the strongest predictor of heterosexual HIV transmission. In this respect, the sexual transmission of HIV-1 is strongly correlated with the concentration of HIV in the partner's blood (Cohen et al., 2011).

In higher income countries, male-to-female transmission is more efficient than female-to-male transmission, although these findings have not been replicated in African studies (Gray and Wawer, 2012). The vertical transmission of HIV from mother to infant, either

[4] Since 1998, AIDS-related deaths have however steadily decreased, as free antiretroviral therapy has become more widely available in the region; decline in mortality may also be an artifact UNAIDS estimate revisions.

[5] Although Lewis (2011) does mention that MSM transmission routes are beginning to attract increasing interest from epidemiologists. See also Price et al. (2012).

in utero, intrapartum or postpartum via breastfeeding, is the second most important transmission route in sub-Saharan Africa. The risk of vertical transmission is approximately 35% and 20% in breastfeeding women and non-breastfeeding women respectively; of the 430 000 children that were infected in 2008, 90% of the cases were the result of vertical transmission (Coutsoudis et al., 2010 citing WHO, 2009). Global differences in HIV prevalence and incidence are further compounded by higher rates of breastfeeding among African women (Bulterys et al., 2002). Although intravenous drug use is quite low in Africa, one in eight users are reported to have contracted HIV through this route (Lewis, 2011). Biologically, blood transfusion is the most efficient pathway for HIV transmission: of those that receive seropositive blood, 90% become infected (Piot and Bartos, 2002). In Africa, HIV acquisition through blood transfusion is the consequence of poverty and the deterioration of health services across the continent. African women and children are particularly at risk of receiving contaminated blood because of transfusion requirements associated with malaria induced anemia, sickle cell disease and obstetric complications. Overall, however, infection via blood transfusion does not constitute a major route of HIV transmission in sub-Saharan Africa.

3.1 A multilevel model of HIV/AIDS

Sub-Saharan Africa is one of the few contexts (alongside Haiti) to experience the emergence of a generalized, self-sustaining, heterosexual HIV/AIDS epidemic (De Cock et al., 2012; Caldwell and Caldwell, 1993). Investigators have presented a number of explanations for the particularly heterosexual dimensions of the epidemic in the sub-Saharan context (Caldwell, 2000; Caldwell and Caldwell, 1996). And sociologists have addressed the broader demographic transitions in Africa, changes to the cultural and social institutions of African communities, and the reorganization of social life and behavioral relations since the mid-20$^{\text{th}}$ century (Swidler, 2009; Bongaarts, 2007; Crenshaw et al., 2000; Bongaarts and Watkins, 1996; Morris and Kretzschmar, 1997; Caldwell et al., 1993, 1989).

The incorporation of African societies into the global, economic order—first initiated under the logic of colonialism, and then subsequently in the transition to modernity—is a key theme in this story (Wallerstein and Smith, 1992). During these two historical phases, African communities experienced large-scale disruptions to the established political order,

kinship structure, and indigenous belief systems. These disruptions were systematically exacerbated by the importation of institutionalized education, the introduction of wage employment, and the adoption of Western belief systems. European settlers brought with them the Western nuclear family system, which fundamentally reconfigured the rules of kinship, and changed with it the relations between husbands and wives, between parents and children, and between members of the extended kin and conjugal family (Martin and Beittel, 1987). It is within this terrain of broad social upheaval that the African HIV epidemic is thought to have emerged (Caldwell et al., 1989).

The HIV/AIDS epidemic in sub-Saharan Africa has a complex social history. Efforts to manage the spread of HIV in this context are further complicated by existing traditional and cultural beliefs about disease which are at odds with western medicine; a predominantly patriarchal social structure which constrains the ability of woman to exercise health-seeking behaviors; enduring structural and institutional inequalities which are mainly the historical byproducts of colonialism and racism; and a lack of health-care infrastructure to provide adequate services and medications.

The predominantly heterosexual spread of HIV/AIDS in this context involves the often intimate sexual relations between two people, bringing the issues of interpersonal power, inequality, and dependency into play. An adequate explanatory framework of HIV will need to acknowledge the social, behavioral, and biological inputs that have shaped the character of the current epidemic in sub-Saharan Africa. As Gillespie et al. (2007: 12) affirm:

> A major analytical challenge is to define the causal pathways operating from distal socioeconomic factors to proximal individual behaviors and ultimately physiological factors. Different socioeconomic factors may affect health at different times in the life course, operating at different levels (e.g. individual, household and neighborhoods) and through different causal pathways.

In an attempt to get at a better understanding of these multiple causal pathways, I propose a conceptual framework consisting of three levels. These levels are: the community context or the macro-social level; the household relations that are situated at the micro-social level; the individual level, which includes the behavioral and biological determinants of HIV-related outcomes (see Figure 3.1). I make reference to this conceptual model in the empirical chapters, where I present an analysis of the preventive and survival benefits of

ART in a rural South African community. Briefly, my starting assumption is that macro-social forces define and shape social relations at the household level, before being mediated by the proximate determinants.

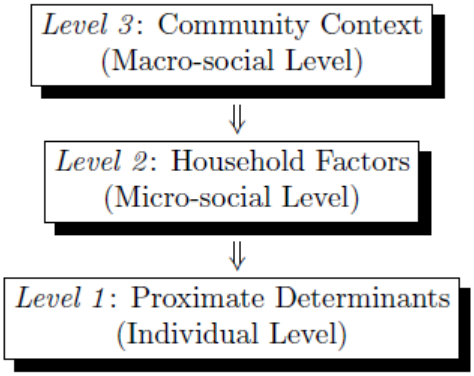

Figure 3.1: Multilevel Model for HIV-related outcomes

A unique contribution of this chapter is my conceptual treatment of the household factors associated specifically with HIV acquisition risk. Households are conceptually important components in the proposed multilevel model because of the range of integral functions that take place within this domain. A household can be defined as a group of persons that share a home or living space, and who aggregate and share their resources (Scott and Marshall, 2009). These functions may include among others, socialization processes, union formation, marriage, birth, childbearing, resource allocation, death and dissolution. I choose to focus on social relations of the household because, unlike other health-related behaviors (such as smoking, obesity, alcoholism) or infections diseases (the spread of measles or influenza through casual contact), HIV infection or transmission involves two or more people and the (often intimate) links between these two people. The predominantly heterosexual spread of HIV in this context therefore compels us to consider the sorts of social things that help HIV get into the body. Heimer (2007: 566) explains this objective quite well when she writes that "[w]hat happens inside the body may be a biological matter, but the [HIV] virus's journey between bodies in blood, semen, and breast milk is both biological and social." The exchange of bodily fluids within the household settings are shaped and defined by the broader social institutions of marriage and fertility.

For this reason I concentrate on the social relations of the household, since this is the level where i) decisions about fertility and sexual interaction are enacted, and ii) where the broader influences of societal factors are mediated. This point is partly informed by Easterlin (cited in Smith, 1989: 176), who argues, in the case of fertility, that a framework be "developed at the level of the couple or household since it is assumed that they are the ultimate decision makers about fertility", and if the "community or society desire higher or lower fertility, they must somehow influence couples or households."

Social relationships matter because in a multilevel model of health, the household level variables must mediate the community level influences on individual level behaviors. This assumption is based on the hierarchical relationship between the community and household contexts. Households that are located in a local community (community A, for example) will tend to be more similar with one another than households from different local communities (communities B, C, D, ...). Here the community level is seen to shape and configure household characteristics related to resource allocation mechanisms, domestic productivity, and the social relations between household members. In addition, the social relations between household members are further defined by the systemic allocation of resources and opportunities within the household, which ultimately shape existing relationship structures and processes within the household. I argue that it is at this level that the broader, community factors related to power, control, inequality and economic dependency enter into the lives of individuals, which either enhance or suppress the risk of HIV acquisition.

An important question that must be accounted for in a multilevel model of HIV acquisition relates to whether household level factors play the role of main or buffering effects. Positioning the household level between the cultural context and the individual outcomes level therefore provides us with a useful starting point for investigating the role of household factors (for example, social relationships, socioeconomic position, migration) on exposure to HIV-related risks. Thus, while socio-demographic trends and patterns can be seen to shape contemporary families or households, it is simply not clear how such trends and patterns may influence HIV-related outcomes, without first considering the household functions that mediate them. These household factors must in turn be linked to lower-level individual behaviors, which are defined as the proximate determinants of HIV (discussed in more detail in Section 3.1.1).

3.1.1 A proximate determinants framework of HIV

A proximate determinants framework motivates the attempt to understand the behavioral and biological mechanisms through which social factors must operate to influence HIV-related outcomes. Consider the following simplified example: a geo-political area enters into a period of economic decline, significantly increasing the unemployment rate within a local community. In response to this economic crisis, males—a large proportion of which are household-heads—migrate in search of employment opportunities outside their immediate social network. The migrant subsequently gains access to new social networks, characterized by high HIV prevalence in urban areas (Abimanyi-Ochom, 2011). At this point, no valid causal mechanism has been offered for the evidence that links migration with an increased probability of HIV infection or transmission. To complete the causal chain, this male actor (in our thought experiment) must engage in some or other behavior, typically, risky sexual behavior, that is conditional upon his entry into a new social network, before he is infected with HIV. Because of the distance between the male household-head and his partner, we can then begin to unpack the set of household level variables that result in the increased risk of HIV acquisition for the female partner who has thus far remained in her local community.[6]

The macro-social (economic decline, the onset of poverty, unemployment) and the micro level (the type of partnership and migration) factors must, by definition, be identifiable and antecedent to the proximate determinants of HIV transmission and acquisition. For example, out-migration may introduce an individual to new social networks and sexual partners—in the absence of household constraints—which increase the number of sex partners acquired, concurrency, and sexual mixing. These behavioral changes consequently affect the biological determinants of HIV infection or transmission. The probability of HIV acquisition at the household level is increased upon the male partner's return, due to the local household network structure and the degree of closeness between the couple.

Boerma and Weir (2005) present a proximate determinants framework of HIV transmission. As with the approach to fertility, we can think of there being a set of proximate determinants through which the social determinants must operate in order to influence the

[6] In network analysis, closeness is defined as the distance between two social actors, which refers to the number of ties between actors (and not necessarily geographical space), which in the case of a conjugal partnership is a value of one (Wassermann and Faust, 1994).

probability of HIV transmission. The authors identify and list the HIV proximate determinants in Figure 3.2. The proximate determinants link the set of social factors (underlying determinants) with the biological determinants, which are identified as 1) the exposure of susceptible to infected persons, 2) efficiency of transmission per contact, and 3) duration of infectivity. Reducing any of the biological determinants to zero implies, by definition, that there is a zero probability of HIV transmission.

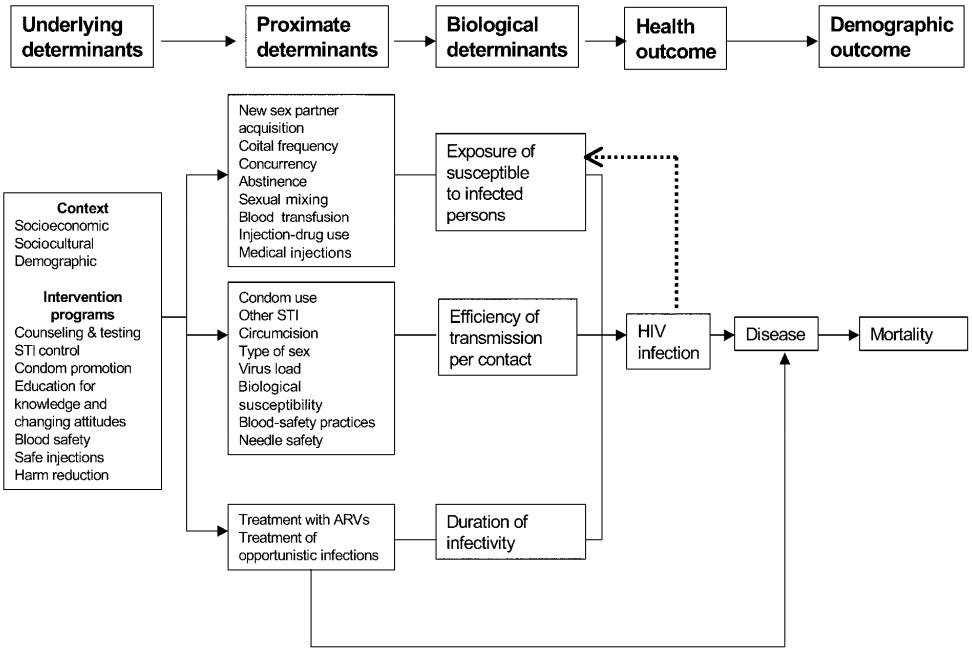

Figure 3.2: The Determinants of HIV Transmission (Boerma and Weir, 2005)

The social or underlying determinants, which refer to the socioeconomic, demographic and epidemiological characteristics of a community, must operate through the proximate determinants in order to influence HIV transmission. The proximate determinants, defined as either biological or behavioral variables, have direct links to the biological determinants. Increasing or decreasing values on one or more of the proximate determinants (while holding the remaining determinants constant) varies the probability of HIV transmission. For example, Bloom et al. (2002); Auvert et al. (2001) and Fortson (2008) show that circumcision has a strong protective effect in men by reducing the transmission efficiency of HIV. The

presence of an STD (Gillespie et al., 2007), and the longer an infected man remains with and STD (before seeking help) the more likely he is to have had unprotected sex (Langeni, 2007), thereby increasing HIV transmission efficiency. Men who pay for sex are more likely to increase the values on the behavioral proximate determinants of sex partner acquisition, coital frequency, concurrency and sexual mixing, thus increasing the biological determinant of exposure of susceptible to HIV-positive persons (Lewis et al., 2007). Poor socioeconomic status may constrain a mother's health-promoting choices for her infant, leading to continued breastfeeding and an increase in the probability of the vertical transmission of HIV from mother to infant (Rollins et al., 2008).

Lewis et al. (2007) argue that without developing a conceptual framework, confusion about the relevance and influence of social and behavioral variables on HIV outcomes is likely. Identifying who is at risk, and why, is generally complicated because of the range of behavioral decisions that place individuals at risk of infection, the heterogeneity of risks within a susceptible population, and the complex social norms which govern sexual behavior. In their study, Lewis et al. (2007) define the proximate determinants as describing individual behavior as well as characteristics of the partner or partnership. In their results, the authors conclude that the most important proximate determinant was lifetime number of partners for both men and women.

Bärnighausen and Tanser (2009) inform us that further work still needs to be done on the factors that determine epidemic spread, and to explain why sub-populations experience different epidemics. In sub-Saharan Africa, the HIV epidemic is characterized by a "series of interlinked subepidemics that operate within different social and geographical spaces" (Bärnighausen and Tanser, 2009: 436). For this reason, it is important to distinguish the factors that shape an individual's sexual behavior from the factors that determine the level of infection in a community from which an individual is likely to choose a sexual partner. Generally, risk-related or health-promoting behaviors cluster within certain communities, which are likely to predispose individuals to corresponding health outcomes. Bärnighausen and Tanser (2009: 437-438) address some limitations of the framework by Boerma and Weir (2005) by suggesting the following:

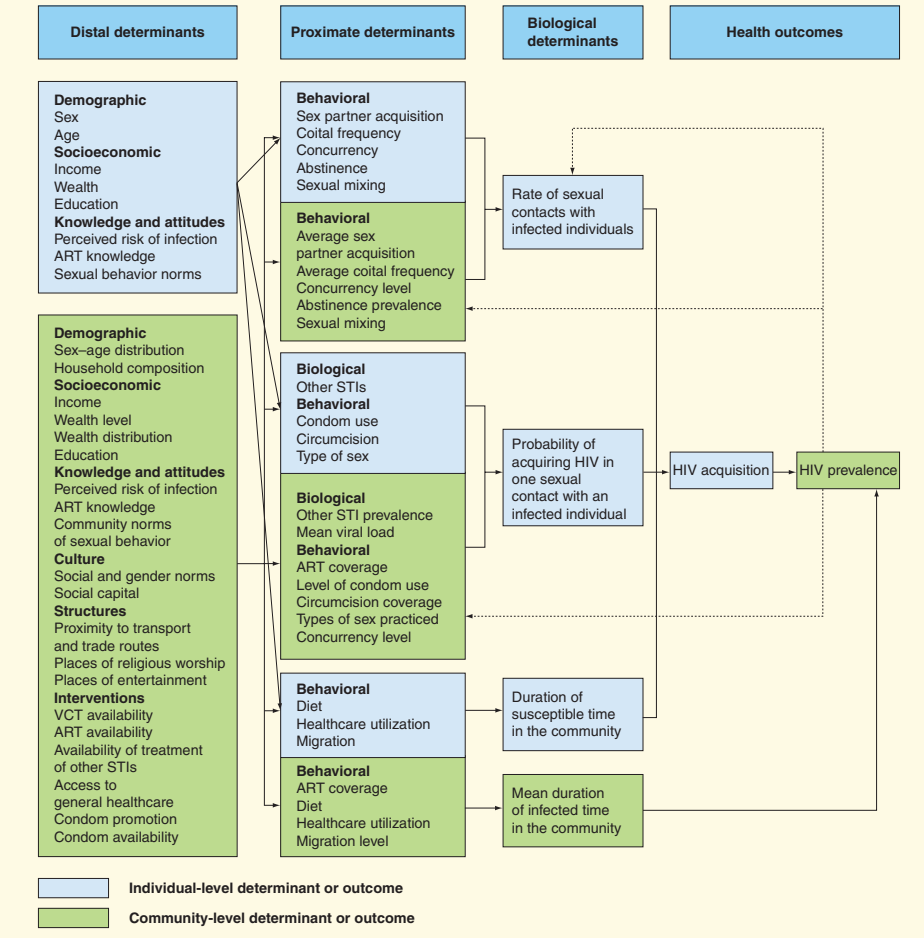

Figure 3.3: The Determinants of HIV Acquisition (Bärnighausen and Tanser, 2009)

1) They prefer the use of HIV acquisition rather than HIV transmission as the outcome, on the basis that the former is an easier measure to obtain given the availability of comprehensive molecular databases. They define this new set of biological determinants as a) duration of time in the community, b) rate of sexual contact with infected individuals over time, and c) the probability of acquiring HIV during one sexual contact with an infected individual. These three biological variables are functions of the proximate determinants.

2) By further elaborating upon the underlying or community level determinants: many of the individual level determinants have community level counterparts, which can be constructed by aggregating the characteristics of the individuals who comprise the community.

The proximate determinants at the community level capture the various aspects of HIV transmission. Although the person transmitting is usually not known in the dataset, the proximate determinants of transmission can be determined at the community level.

3) A proximate determinants model must include feedback loops from HIV acquisition to the proximate determinants of HIV acquisition. As HIV prevalence increases (a health outcome), individuals may begin to adjust behavior, such as reducing sex partner acquisition and concurrency (which are the proximate determinants) thereby reducing the rate of sexual contact with infected individuals.

3.1.2 The household context

I have thus far outlined the role of the proximate determinants in a multilevel model of HIV acquisition. In this section I will argue that household level variables be considered as an important set of mediating variables that are situated between the community context and the proximate determinants. I will proceed to outline how household factors can be incorporated in a multilevel analysis of HIV acquisition.

The term household is a broad concept which defies a definitive conceptual definition. In the social sciences, different disciplines have focused on particular aspects of the household structure and its functions. For example, social anthropologists have stressed the kinship dimensions of social life, and have preferred to focus on the relations between the family and the household (Caldwell et al., 1993, 1989). Perspectives orientated around economics have defined the household as a unit of production and consumption, with particular attention devoted to the division of labor and the allocation of resources within this domain (Becker, 1974). Feminists have brought attention to gendered aspects of the household, focusing particularly on the socially defined and prescribed roles in the interaction between men and women (See for example, Ferree, 1990).

Adding further complexity to this conceptual formulation is the difference in types of ties, links or relations between family members between the West and other geo-political contexts. Attempts to arrive at a precise definition of the household and family system is not a matter of mere academic curiosity; rather, identifying the prevailing urban family system, and the boundaries of the household, constitute the very practical business of modern states and the market (Becker and Murphy, 1988). It is through the household

that essential information about the population is collected. In the West, the household is an attractive starting point for this objective, since it is operationalized to be a self-contained unit that is relatively easy to identify, sample and access. Ideas of the household as a site of production and consumption further provide state bureaucrats, demographers, economists and entrepreneurs with vital data about the behaviors of citizens.

Survey strategies have managed to successfully and systematically collect a wealth of information on Western households. This is because of the specific characteristics of the household that make it amenable to data collection methods. The Western household is typically operationalized as a (a) discrete and (b) bounded, (c) residential unit with (d) an unambiguous membership (e) centred about a conjugal couple and (f) for a while, their minor dependent offspring. It is (g) invariably a unit of consumption in which (h) all income may be shared but some pooling of income must occur" (Russell, 2003a: 8).

This methodological framework of survey sampling is heavily centered on the conception of a Western conjugal nuclear family system. This conceptualization relates to more than simply the size or composition of the household, it also refers to the structural and relational components that describe the cohesion and mobility of household members. These observations have prompted researchers to question whether Western formulations of the household can effectively capture the social reality of kinship systems and households in other parts of the world (Wilk and Miller, 1997). Failure to consider and appreciate these structural and functional characteristics may threaten the validity of inferences made about households that do not particularly meet the definition of the Western conjugal nuclear system.

Russell (2003b) has discussed this issue in some detail, and has drawn attention to the set of problems that derive from the collection of information from southern African households. These problems stem from a set of characteristics that differentiate the family and household systems of the West from sub-Saharan Africa. As an ideal-type, the defining feature of the Western household is its bilateral mode of descent. In this system neither the wife's nor the husband's family takes precedence over the other; the couple each have their own constellation of close relatives, and there is usually no overlap of kin between the two families. A partner thus passes through life with access to two conjugal family households: the one into which he or she was born, and the one to which he or she married. Typically, marriages are between two people of the same age. Once married, the couple

establish their own independent household to raise their children to maturity. In the West, then, the household is centered around the tightly-connected couple, and the greater (if not all) share of decision making regarding the rearing of their children is made by the parents. For this reason, the conjugal-nuclear system and the household are sometimes considered as one and the same thing.[7]

In sub-Saharan Africa, the family system is predominantly unilineal, with descent through the father (Caldwell et al., 1993; Goody, 1973). This system establishes the formation of identities, determines who resides where and with whom, and favors the reproductive preferences of the husband. African culture bestows upon men considerable power in household affairs and, more specifically, in the reproductive decision-making process (Dodoo, 1998). For this reason, demographers have begun to pay greater attention to the role that male household-heads play in the inability of women to translate their reproductive and sexual health goals into reality. Marriages are typically between an older man and a younger women. Fertility is of great importance, and marriage is the right to a woman's fertility; women bear children for their husband's lineage. For example, Dodoo (1998) observes that the purpose of the traditional payment of bridewealth from the groom's family to bride's family is to compensate the bride's family for future births which will become part of the groom's lineage. In this respect, children will belong to the patrilineage of the man who impregnated their mother, or they may belong to mother's husband regardless of the impregnator. In contradistinction to the conjugal nuclear system, child bearing is rarely the exclusive responsibility of the parents. African children are more likely to spend a substantial part of their time in the household of either their paternal or maternal grandparents (Russell, 2003b). In many respects, the kinship structure may be considered to be less cohesive but generally more interconnected to a larger kinship system; and high household member mobility may further contribute to the specific character of the African household.

In black households of southern Africa, marriage is not a couple-centered institution, and this is a key distinction in comparison with the Western family system (Russell, 2003b). In this kinship system the lineage bond is emphasized over the conjugal tie, which ostensibly produces a less restrictive relation between a man and a women—and therefore between

[7] See, for example, the Oxford dictionary's definition of the family as a "group consisting of two parents and their children living together as a unit."

a husband and wife—than is typically observed in Western partnerships. Caldwell et al. (1993) observe that emotional links within the African household are weak, and that women are not supposed to inquire of a husband's sexual relations outside of marriage. Husbands are generally much older than wives, and divorce is fairly common among most ethnic groups. Partners are unlikely to discuss whether they are infected, and the sexual routines and norms do not permit for the identification of STDs in the partner (if sex in undertaken in the dark, for example). Many non-symptomatic persons do not know of their STD or HIV status, and for women there are costs associated for disclosure (i.e., accusations of infidelity). High levels of polygamy are also features of the household structure in certain areas south of the Sahara. According to Caldwell et al. (1993), polygamy can only exist if men marry for the first time at an age ten years later than woman, therefore delaying the onset of marriage for men to their late twenties. An implication of delayed marriage is the high proportions of unmarried post-pubertal men whose surplus sexuality is absorbed into the extended family, or into relations with widows, deserted wives and polygamously married women not receiving support from older husbands.

Caldwell et al. (1989) argues that the basic social system, and consequently the basic family unit, in sub-Saharan Africa is a mother and her children. Considerable marital instability, high divorce rates, husband mobility, and the emphasis of lineage over spousal links result in high levels of female headed households.[8] Female-headed houses are also largely the product of male out-migration to urban areas in search of employment and income. Male out-migration increases exposure to new sexual opportunities, on the one hand, and a diminished capacity to control the movement and decisions of women back at home, on the other. These factors have contributed extensively to the nature of the HIV/AIDS epidemic in the sub-Saharan context. The epidemic has been driven by factors relating to a higher level of sex outside marriage, and higher levels of transactional sex and prostitution due to the concentration of men in urban areas. STDs which are important cofactors in the transmission of HIV, are prevalent and are accompanied by a low rate of safe sex practices undertaken in households dominated by male decision-making.

[8] The consequences of single-headed female households are nevertheless less consequential than in Western societies. Here, household arrangements are secondary to the essentials associated with the female's patriclan name, which guarantees to her entitlements and claims to a share of the paternal homestead.

The particular structure of the household, and the relations between the extended kin network, are important considerations that must be accounted for in the study of HIV/AIDS. Furthermore, identifying the household level factors may help us to more carefully assess the relationship between socioeconomic status and HIV risk. Socioeconomic status may be uniquely reflected among the various components of the particular household structure, and the relations between members of the household. Including household level factors in a multilevel model of HIV infection means that we can continue to incorporate the constructs of hierarchy, power, control and inequality in an analysis, as was the case in the reviewed discussion of socioeconomic position. These constructs are infused into, and permeate, the household network, and therefore characterize the relations between household members. Because the exercise of power is ubiquitous, it may be useful to speak more specifically about the various aspects of social relations at the household level, and how these aspects may expose individuals to the risky behaviors that result in HIV transmission or acquisition. As a point of departure, it would be useful to partition this relatively broad concept into the dimensions of type of relation, contact frequency, duration of contact, multiple membership, empowerment, partnership cohesion, socioeconomic status, household network, composition, and formation/dissolution.

Type of relation: This is a property that describes the linkages between two or more household members. Of particular interest are the types of partnerships—marital, conjugal, non-conjugal and casual—between actors that include sexual relations. As is discussed in the section below, partnership or union type is closely related to relational aspects of power and control. Past research has suggested that attention continue to be devoted to evaluating differences in HIV risk by partnership or relationship type. For example, Abimanyi-Ochom (2011) and Auvert et al. (2001) report that women who were ever married, widowed, and divorced were more vulnerable to HIV acquisition than the never married. Langeni (2007) report that being married and having had sex with more than one partner in the last 12 months multiplied the odds of having had unprotected sex by three times. Bloom et al. (2002) report that marital status was the strongest risk factor for HIV seroconversion, with those formerly married four times more likely to be HIV-infected than those who never married. Auvert et al. (2001) report that a higher frequency of unprotected sex may also take place in a marital unions than in casual relationships. In his paper, Reniers

(2008) discusses how individuals use marriage as a resource with which to manage exposure to HIV, either through mechanisms of negative or positive selection. Negative selection mechanisms may include marriage to a partner who has HIV, or who is likely to commit adultery. Reniers finds that those who use positive selection mechanisms for remarriage are less likely to be infected than those who remain single.

Frequency of contact: This describes the strength of social ties, and includes a measure of the degree and quality of contact and interaction between household members. Mobility, travel or migration are considered to be useful proxies for the measure of frequency of contact. In sub-Saharan Africa, "the traditions that regulate sexuality and marriage are disrupted by employment practices that take men away from home for extended periods" (Heimer, 2007: 570). Travelers are more likely to have a higher levels of partner acquisition, because of the mobility afforded by a higher socioeconomic position and occupational opportunity (Morris et al., 2004). Here travel is seen to weaken social constraints and increase exposure to new sexual partnerships which increase the proximate determinants of multiple sexual partners and coital frequency. Migration results in bridges to other networks, characterized by higher HIV prevalence among sex workers or in urban areas, for example. Thus, frequency away from the household, duration of time away from the household, the frequency and duration of return visits may be important indicators of HIV risk. The type of relationship between household partners will also have something to say about the frequency of contact, including sexual contact. For example, research has shown that consistent condom use is less likely with a regular than a casual partner (Chimbindi et al., 2010).

Empowerment: Feminist scholars have drawn attention to the traditional and patriarchal structure of the household in South Africa (Shisana et al., 2010; Albertyn, 2003) and elsewhere (Borovoy and Ghodsee, 2012; Brines, 1994; Sorensen and McLanahan, 1987), which results in the inherent inequality of its female members. A patriarchal hierarchy typically confers power to the male household-head, enabling him to regulate and control the behaviors of other household members, as well as to determine the allocation of resources within the family (Ulin, 1992: 63; see also Iyayi et al., 2011; Orubuloye et al., 1993). Women who do not have access to independent capital and resources are often forced to depend on alternative strategies to procure goods, which may push some women to form unions with

economically independent men or to engage in transactional sex. This power differential is further compounded by the social norms which favor men in terms of control over sexual decision-making (Jewkes et al., 2010; Kalichman et al., 2005). As a result, women who are economically dependent on their partners may not be able to insist on condom use and safe sex practices (Gillespie et al., 2007). The social norms governing sexual behavior in sub-Saharan Africa often imbue men with greater freedom to engage with multiple sexual partners (often younger women) and to dominate or control sexual decision making.

Aspects of household relations that reflect power and control may be important social determinants of HIV outcomes. Research has shown that disempowerment, economic dependency, structural violence, low socioeconomic status, and the failure to negotiate safe sex practices are associated with a higher probability of HIV acquisition, particularly among women in the developing context (Luke et al., 2011; Bandali, 2011; Hawkins et al., 2009; Luke, 2003).

> Because many women are economically dependent on men, the degree to which they are able to express their own will is often limited. This lack of choice—or lack of power—leads some women to engage in high-risk behaviours, which increases their chance of contracting the HIV virus (Opportunity International, quoted in Wojcicki, 2005: 4).

Measures of empowerment and control are methodologically difficult to obtain with surveillance data. Wojcicki (2005) suggests that socioeconomic status and education can be used as two proxy measurements for empowerment. In a review of the literature, Luke et al. (2011: 1050) report that women's wage labor and income is positively associated with decision making about household expenditure and the use of contraception; and that "women who worked for cash had more power to negotiate the timing and frequency of sex with their husbands than nonworking women". Disempowerment refers to women who do not have access to independent capital and resources, and who therefore depend on alternative strategies to procure goods, which may push some women to engage in transactional sex or to form unions with economically independent men.[9] Dependency on men for

[9] Leclerc-Madlala (2008) discusses that women may express agency in their choice of older men as this is an act of self-assertion, cleverness and an important contributor to self-perception of modern, sexually-liberated women.

economic transfer reduces the bargaining position of women, and ultimately their capacity to engage in protective sexual behaviors. In their studies, Davidoff-Gore et al. (2011) and Abimanyi-Ochom (2011) show that young people and women with greater economic resources, and hence increased decision-making power, were able to successfully negotiate condom use in their relationships.

In developing countries, women generally have limited access to educational resources. Education may be further linked to employment status, access to resources, greater mobility and hence increased autonomy and independence. A number of studies have investigated the relationship between education and HIV risk. For example, Davidoff-Gore et al. (2011) report that inconsistent condom use is associated with a lower level of education, lower amounts of income and larger amounts of money and gifts received from sexual partners. Glynn et al. (2004) found that more educated persons reported less frequent sexual behavior. More highly educated women were less likely to report a lack of control in sexual relationships and less likely to use condoms inconsistently (Weiser et al., 2007); better off women reported fewer partners and were less likely to engage in transactional sex (Lopman et al., 2007). Wojcicki (2005) notes that a some studies show a positive association between higher socioeconomic status and increased HIV risk. More funds for some women may actually increase exposure through greater access to partners or opportunities for travel. Higher educational status may also make some women more mobile, access better jobs and therefore gain access to partners with higher mobility.

Partnership Cohesion: Closely related to the household component of empowerment is partnership cohesion. Partnership cohesion measures the quality of social relationships which, depending on the kinds of behaviors, may be either health promoting or health damaging. Whereas empowerment indicates the capacity of individual household members to negotiate protective health behaviors, partner cohesion refers to the various aspects of an intimate sexual relationship that vary the risk of HIV acquisition. Union, partnership and marital relations are often considered to mediate health outcomes, an important observation particularly in the context of HIV/AIDS. The degree of integration, stability, and symmetry typically describe the characteristics of a sexual partnership between two household members (usually between the male household-head and his partner).

Within the general population, there is a tendency toward homophily, or assortative mating where prospective partners are chosen on the basis of similarity (symmetry), and where partners are selected from within their social networks (Kalmijn and Vermunt, 2007). In network theory, symmetry (or homophily) is thought to result in strong ties reducing the potential for transitivity—the ability of weak ties to reach across to clusters that may be characterized by high HIV prevalence (Aral et al., 2004). A strong network structure, characterized by "small size, strong ties, high density, high homogeneity, and low dispersion appear to be helpful in maintaining social identity and hence health and well-being" (House et al., 1988: 304). In this sense, larger networks with weaker ties, greater heterogeneity and higher dispersion are likely to produce greater changes in health and well-being, which in the context of a high prevalence HIV epidemic, may ultimately increase the exposure and efficiency of HIV transmission and infection.

It is worth noting that the issue of gender is central to this discussion of the relational aspect of economic and partner symmetry. Research has shown that partnerships characterized by a high level of stability, integration, and symmetry buffer the household from HIV-related risks. The aspect of partnership cohesion to receive the most attention is age symmetry because of higher HIV prevalence among older men, and the gender-based power differences in age disparate relationships that reduce the ability of younger female partners to negotiate safe sex practices (Leclerc-Madlala, 2008; Luke, 2003). Age disparate relationships are generally defined as an age gap of greater than 5 years between a female (usually the younger) and male partner. Langeni (2007), for example, showed that for every year's increase in the age difference between partners there was a 28% increase in the odds of having had unprotected sex. In their work, Chimbindi et al. (2010) discuss how having a partner older by at least a year significantly reduced the likelihood of using a condom compared to partners of the same age. Age asymmetry may be further correlated with *relationship type*. In their study, Ott et al. (2011) report substantially larger age differences in spousal relationships than in casual relationships.

Partner stability within the household may also be an important factor in HIV risk. As discussed in the previous section, relation type is associated with HIV risk, while partner stability characterizes the quality of the partnership. A number of studies have looked at the behavioral and sexual practices associated with partner stability. Shai et al. (2010: 1383)

report that South African women (in the Eastern Cape province) with only one partner had a much more equitable power distribution in their relationships, which facilitated condom use; results also showed that condom use was enhanced by the relative stability of having only one partner. Pulerwitz et al. (2002) discuss how greater equity in a relationship increases a woman's ability to use condoms; whereas women in poorly perceived relationships reduced opportunity for discussion and negotiation of condom use (Jewkes et al., 2003). However, Chimbindi et al. (2010) report that condom use declined with the formation and duration of stable relationships—a finding that corresponds with decreased condom use in marital relations compared with the never married (Bloom et al., 2002; Auvert et al., 2001).

Among asymmetric or discordant partnerships, communication may be challenged and likely involve precepts of power, inequality or control. Kohler et al. (2007: 27) find that "social networks influence not only the perception of AIDS risks but also important household decision processes in the adoption of preventative behavior." They also report that increased interaction between partners tended to increase discussion and communication about HIV/AIDS, thereby informing safer sexual practices. Households characterized by partner absence, relationship discord, and large differences in income are associated with increased probability of HIV infection (Ott et al., 2011; Reniers, 2008; Kohler et al., 2007; Luke, 2003). Factors relating to fear of divorce or abandonment may affect motivation to disclose one's status, which has strong implications for the adoption of protective behaviors against HIV risk and transmission. Gender based violence and fear of physical abuse may prevent disclosure for fear of reprisal (Anglewicz and Chintsanya, 2011). Furthermore, union instability and discord may lead to heavy sexual mixing with two or more partners outside the household network, thereby increasing in the proximate determinants of concurrency, coital frequency, and multiple sexual partners.

Socioeconomic status: It is generally acknowledged that studies of HIV acquisition and spread in sub-Saharan Africa are undertaken in areas characterized by "relative poverty in the context of generalized chronic poverty" (Gillespie et al., 2007: 6). In this context, the relationship between socioeconomic status and health is quite dynamic and complex. Gillespie et al. (2007) report a weak positive relationship between national wealth and HIV

prevalence across the continent. Countries with a good transport infrastructure, strong urban-rural linkages, and high professional mobility have a higher HIV incidence rate.[10]

A number of studies have reported a positive association between socioeconomic status—when measured as either wealth or education—and HIV acquisition. A substantial body of research has argued that higher levels of education and wealth generally lead to greater personal autonomy and mobility, thereby increasing the demand for sexual partners and heightening the risk of HIV infection (Ho-Foster et al., 2010; Glick and Sahn, 2008; Gillespie et al., 2007; Hargreaves et al., 2008; De Walque, 2006; Shelton et al., 2005; Wojcicki, 2005; Hargreaves and Glynn, 2002). In her study of five African countries, Fortson (2008) found that better educated respondents were more likely to have engaged in premarital sex and have a positive HIV serostatus. In their work, Msisha et al. (2008) link higher disposable income and increased mobility in wealthier neighborhoods to high-risk behavior and involvement in multiple sexual networks. Generally, increases in economic resources, occupational opportunity, education and mobility, along with pre-existing behavior patterns, tend to make the wealthier social groups more vulnerable to HIV infection, despite better access to health resources (Gillespie et al., 2007).[11]

The socioeconomic status of a household is theorized to be closely associated with individual exposure to HIV acquisition. The socioeconomic status of a household can determine the degree of access to, and control over, resources which in turn can be used to minimize or avoid HIV risk. Such resources may include forms of social, emotional or informational support, economic aid and security, and care-giving. These characteristics can be measured by the wealth index of a household, the socioeconomic status of the household-head, and reported social support mechanisms (Loewenson et al., 2009). Empirical studies have shown an association between household socioeconomic status and risk of HIV. Gillespie et al. (2007: 9) report on studies which show that for girls, sexual debut is earlier in poor households (particularly those that experience an economic shock); one study in Kenya shows that asset poverty is significantly related to risky sexual outcomes including early sexual debut, multiple sexual relationships. Women in wealthier households reported higher

[10] Structural differences between countries, and political commitment to intervention programs, may significantly account for between country HIV incidence and prevalence variation (Robinson, 2011).

[11] This relationship may have begun to change over time, along with the changing dynamic of the AIDS epidemic. Further research is needed to ascertain whether more wealthier social groups have begun to adopt safer sexual practices in light of increased public awareness and educational interventions.

condom use, although professional women (in Kenya and Uganda) were at higher risk of HIV infection than non-professional women (Abimanyi-Ochom, 2011). In a study of women in Botswana, women who earned more or the same as their partner were reported as having at least one sexual partner in the last month (Ho-Foster et al., 2010).

In their study, Bärnighausen et al. (2007) examine the relationship between socioeconomic status and HIV seroconversion risk, specifically with respect to the hypothesis that a decrease in socioeconomic status may increase the risk of HIV infection. The authors argue that household wealth and expenditure capture different financial aspects of socioeconomic status. Wealth is considered to be a more sensitive measure of long-term socioeconomic position, and is measured through a household asset index which include items such as house ownership, water source, toilet type, electricity, household goods, and livestock for example. Households were categorized as belonging to poorest 40%, middle 40% or wealthiest 20%. Household expenditures capture the short-term financial liquidity of members in the household, which may determine how behaviors are regulated or constrained in terms of access to treatment (of STDs, for example), travel, spending (on rent, shopping, electricity, transport, telephones and bills, etc.). The authors report that members belonging to the middle category of the relative wealth index, rather than the poorest category, were at greater risk of HIV acquisition (Bärnighausen et al., 2007). Chimbindi et al. (2010) report that increased condom use is associated with belonging to a household with a high socioeconomic status. Importantly, belonging to a family with a middle or high socioeconomic status is associated with increased condom use among young adults. In their study, Davidoff-Gore et al. (2011) found that households in the third and fourth wealth quintiles had a greater odds of inconsistent condom use. These results support earlier research that young men and women in households with lower wealth are more likely to use condoms inconsistently, compared to those in wealthiest households.

Hallman (2005) explore how the relative household wealth index influences the sexual behaviors and experiences of young men and women aged 14-24 years. She finds that females residing in a low-wealth household were more likely to have an earlier sexual debut, a greater chance of having a non-consensual sexual debut, and have a higher rate of physically forced or exchanged sex. Low wealth for females was also associated with having multiple sexual

partners and a lower chance of condom use at last sex. Low wealth also reduced the discussion about safe-sex practices for both men and women.

Household network: This refers to the linkages between individuals with whom one has close relations or affection, which naturally includes family members within the household (Due et al., 1999, see also Hawe et al., 2004). A type of *dyadic* relation may exist between a key/central actor (a household-head) and another similar actor (a partner), or may involve a *two-mode* relations with a different set of actors (i.e., non-household members such as sex-workers or a non-conjugal partner).

Household composition: An important aspect to consider is household composition, which may describe a conjugal-headed household, a single-parent household, a grandparent-headed household, an orphaned household, or a household containing both close and extended kin. The unique composition and formation of the household may directly affect the allocation of, or access to, resources and economic opportunities.

Formation and dissolution: The formation and dissolution of the household over time refers to the addition (e.g., births) as well as the loss (e.g., deaths, permanent out-migration) of household members. The loss of a member may present a significant shock to the household, reducing a potential source of income, and compromising the stability and protective effects of an integrated household against hazardous behaviors. A newborn may place a burden on household resources, although increased family size may offer the potential of additional income sources.

Household level factors are important because they are theorized as antecedent to the patterns of sexual mixing that typically result in behavioral exposure or protection from HIV infection. Households are one way of seeing forms of social organization in action, and they reflect the broader, macro-social norms and values, which are subsequently reinforced and infused into the linkages between household members. It is at the household level that social power and control is exercised, particularly over sexual relationships and risk taking. As stressed throughout this paper, social networks are in turn connected to broader social and community contexts. Such societal factors, whether they be demographic or epidemiological (our macro-social level in the proposed model), determine the conditions and opportunities for the formation of social and sexual relationships, and thus the risk of HIV acquisition.

3.1.3 The community context

The community context is conceptualized as a macro-social level, and is the highest-order level. I propose that four variables can be used to capture community level effects. These are: 1) social attitudes and beliefs, 2) institutions and structures, 3) epidemiological conditions, and 4) demographic characteristics.

Social Attitudes and beliefs: Collective attitudes and behaviors are generally the product of larger, normative social forces operating within the prevailing community. Misinformation about HIV/AIDS, for example, can often emanate from cultural sources of explanation (Kalichman and Simbayi, 2004; Gottlieb et al., 2009). Community stigmatizing attitudes toward HIV-positive persons, acceptance of behaviors involving multiple partner acquisition or concurrency, and resistance to condom use, are likely to be informed by traditional beliefs about health, illness, and death that are at odds with a western medical perspective (Visser et al., 2009; Kopelman, 2002; Forsyth et al., 2008). These community level attitudes and beliefs are acknowledge here because they can strongly influence the HIV-related behaviors of individuals.

Proximity to physical or bounded structures: The spatial proximity of individuals to institutions or structures identifies the second community level determinant. Examples can include distance to health resources (clinic or hospital), transport routes (local road or national highway), socioeconomic resources (school, urban area with occupational opportunities), or entertainment (drinking establishment, sports venue). Additional research has shown strong links between geographic and institutional characteristics and HIV incidence and prevalence (Tanser et al., 2009). Bloom et al. (2002) and Feldacker et al. (2011) report that there is a strong relationship between type of community and HIV incidence, not explained by individual risk factors.

Epidemiological condition: The epidemiological condition of a community can be an important determinant of an HIV-related outcome at the individual level. For example, the level of HIV prevalence in a given community will indicate the probability at which an individual will select an infected partner; or differences in community HIV incidence will place individuals at a differential risk of HIV acquisition (Bärnighausen et al., 2010; Auvert et al., 2001). The level of ART coverage in the community has been shown to provide a protective effect against individual HIV acquisition (Tanser et al., 2013).

Demographic Characteristics: These include, for example, the wealth, income, and education characteristics of a community, and migratory patterns in and out of such a community. Bärnighausen and Tanser (2009: 438) argue that many demographic characteristics are typically the counterparts of the proximate determinants situated at a lower level in the proposed hierarchical model. These demographic characteristics can be obtained by "summing the characteristics of individuals that make up the local community." On the other hand, the demographic characteristics may be some property of the community that is unique to it, and is not shared by other communities within a relatively close social proximity.

In this chapter I proposed a conceptual framework consisting of a community, household, and individual levels. My starting assumption is that the characteristics of the community constrain or reproduce social processes within the household, which then operate through the proximate determinants to affect a given HIV-related outcome. I have argued for the need to systematically differentiate the macro-social processes from individual level behaviors because of the complex epidemiology of HIV/AIDS in sub-Saharan Africa. In the two empirical chapters to follow, I use this conceptual framework to inform my analyses of the preventive and survival benefits of ART. I now turn to a description of the study area and the data before moving on to these two chapters.

Chapter 4

Study Background

South Africa has a quasi-federal system, with each sphere of government—national, provincial, and local—having elected political representatives and areas of authority. Following the transition to democracy in 1994, the four Apartheid provinces of the Transvaal and Orange Free State (Boer Republics) and Natal and the Cape (formerly English Colonies) were broken into the nine provinces of the Eastern Cape, the Free State, Gauteng, KwaZulu-Natal, Limpopo, Mpumalanga, the Northern Cape, North West and the Western Cape. South Africa has eleven official languages: English, Afrikaans, Ndebele, Sepedi, Xhosa, Venda, Tswana, Southern Sotho, Zulu, Swazi and Tsonga.

Under Apartheid, the population was classified into four racial groups: Black, White, Indian and Colored. The South African Census and Statistics South Africa have maintained this classification. Blacks comprise 79.5% of the population, while the remaining three groups are distributed as White, 9%; Coloured, 9%; and Indian/Asian, 2.5%.) (Statistics South Africa, 2011). The total population size of South Africa is estimated to be 50.6 million people, of which 52% are female. Gauteng is home to the largest share of the South African population, with approximately 11.3 million people (22,4%) living in this province. KwaZulu-Natal is the second most populated province with 10.8 million people (21,4%). Of the population younger than 15 years, approximately 23% (3.66 million) live in KwaZulu-Natal and 19.4% (3.07 million) live in Gauteng. Life expectancy at birth for 2011 is estimated at 55 years for males and 59 years for females (Statistics South Africa, 2011).

As of 2011, an estimated 14.5% of the male and 23.2% of the female population (aged 15–49 years) were reported as HIV-positive, and the national HIV prevalence estimate for this age group was 18.8% (Department of Health, 2014). In 2010, not one of the of the 52 health districts in South Africa recorded an antenatal HIV prevalence below 8%.

The KwaZulu-Natal province recorded the highest antenatal prevalence at 39.5%, with five districts in that province recording above 40% (Department of Health, 2011).

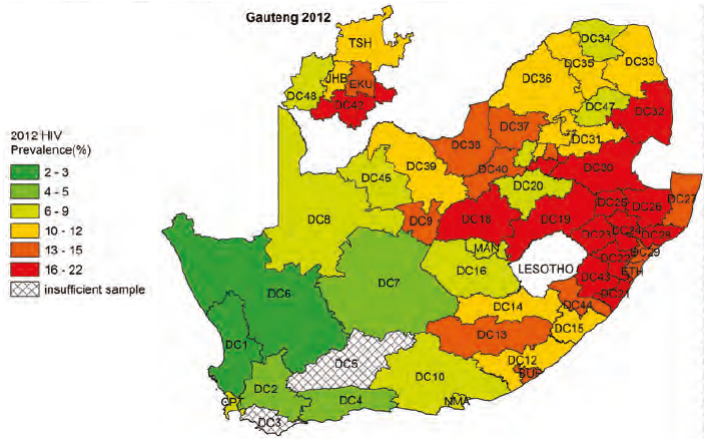

Figure 4.1: HIV prevalence by district, South Africa (Department of Health, 2014).

4.1 Africa Centre for Health and Population Studies (ACDIS)

The Africa Centre for Health and Population Studies was established by the University of KwaZulu-Natal and the South African Medical Research Council in 1997, funded by a large core grant from the Wellcome Trust, UK. In 2000 the Africa Centre Demographic Information System (ACDIS) was started, and in 2003 population-based HIV testing was incorporated into ACDIS. The ACDIS was set up to "describe the demographic, social and health impact of the HIV epidemic [...] and to monitor the impact of intervention strategies on the epidemic" (Tanser et al., 2008).

4.2 Demographic Surveillance Area (DSA)

The ACDIS project is situated in the southern part of the Mpukunyoni Tribal Area of the Hlabisa Local Municipality and the KwaMsane Township and Indlovu Village of Mtubatuba Local Municipality. This area is demarcated by clear geographical boundaries on three sides, making it possible to define exactly the population in what is called the Demographic Surveillance Area (DSA). These boundaries are: 1) the Umfolozi River in the south, 2) the

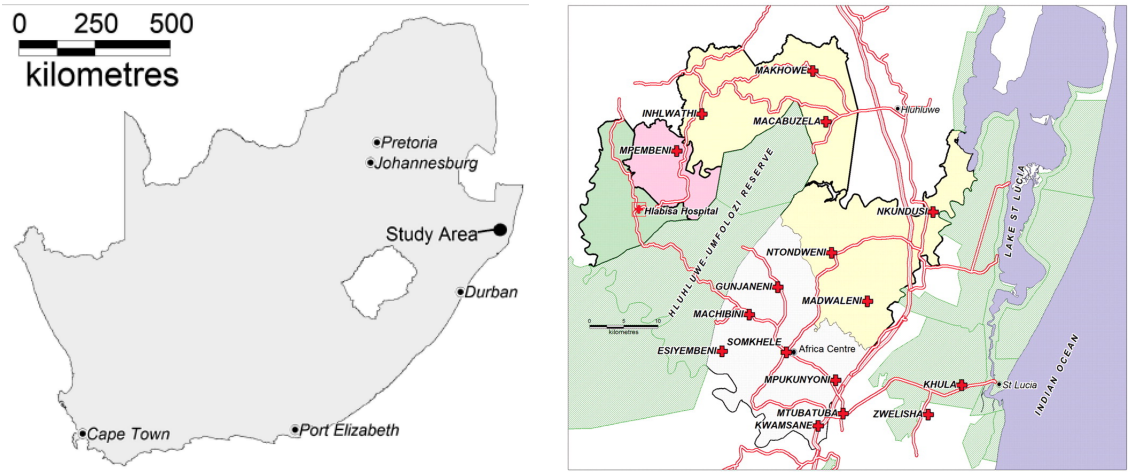

Figure 4.2: Location of study area in South Africa (Tanser et al., 2008; Houlihan et al., 2011)

Umfolozi Game Reserve in the west, and the 3) the N2 national highway in the east. (In the north the boundary for the DSA cuts across the middle of the Mpukunyoni area.) In the eastern section of the DSA, bordering the N2 highway, the DSA is quite flat and densely populated. To the western and northern parts, the DSA becomes increasingly mountainous and thinly populated.

There are three identifiable and different living environments in the DSA: 1) The *KwaMsane township*, which is an urban area, 2) *KwaMsane reserve* which is a peri-urban area, and the 3) *Mpukunyoni tribal area*, which is a typical rural area. The area is 438 km^2 and has considerable variation in population density (around 20 to 3000 /km^2). The resident population of the DSA is numbered at 75,000 although given migration this figure may be closer to 87,000 registered individuals (Africa Center, 2008). The area is predominantly Zulu-speaking and despite its predominantly rural status, the principle income is waged employment and state pensions rather than agriculture production.

4.3 Data collection.

All data for this study are collected by the Africa Centre. The Africa Centre administers household questionnaires every six months to a key informant in the household. Information

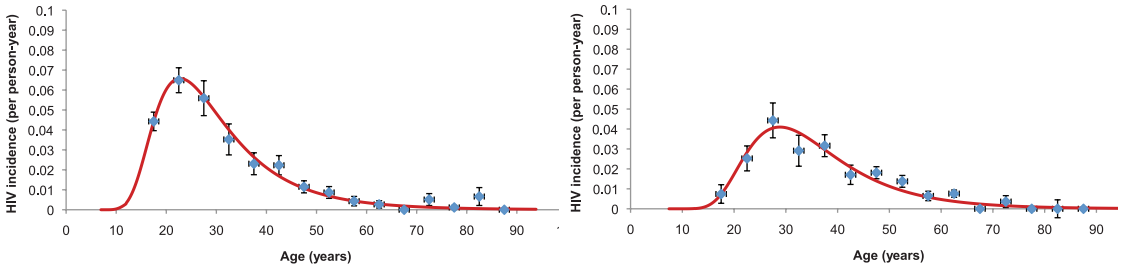

Figure 4.3: Female (left) and male (right) age variations in HIV incidence (95% CI) by 5-year age-group . Superimposed on the graphs are log-normal functions (obtained by maximum likelihood) fitted to the incidence point estimates (Tanser et al., 2013).

is collected on the attributes and events of physical structures, households and individuals and their relationship to one another. The Africa Centre also maintains a geographical information system (GIS) capacity that allows for the spatial analysis of the variables collected. Table 4.2 shows the information collected at the household visit. Nested within the household survey is the population based HIV surveillance survey. This HIV survey is conducted annually and collects information on HIV status, sexual behavior, and other relevant biomeasures by interviewing each eligible household member in person. Table 4.3 shows the individual level data at the start of each year for the period 2004–2012.

Sample/Participants. An individuals must be a member of a household with the study area to be eligible for inclusion in the study cohort, even if he or she is not physically living in the homestead. This cohort includes all women aged 15–49 years and men aged 15–54 years who were resident in the surveillance area and thus eligible for HIV testing. In 2007, eligibility was extended to cover all residents aged >15 years of age. In addition to the resident sample, a 12.5% stratified sample of non-residents ('migrants') was also included in each round of data collection (Tanser et al., 2008).

4.4 Transition of the HIV epidemic

Population based HIV surveys in the study area have shown some of "the highest population based infection rates ever documented worldwide" (Tanser et al., 2008: 960). In 2003–2004, prevalence peaked at 51% (95% CI 47-55%) among women aged 25–29 and 44% (95% CI 38–49%) in men aged 30–34.3. The study area has seen a steady increase in HIV prevalence

from 21.8% (95% CI 20.9–22.7) in 2004 to 29.0% (95% CI 27.9–30.1) in 2011, which has been attributed to the government scale up of ART during this period (Zaidi et al., 2013). Non-resident men were nearly twice as likely (adjusted OR=1.8) to be infected than their resident counterparts; the corresponding ratio for women was 1.5. Geographically, the prevalence of HIV varies from >35 % in informal settlements near the N2 highway to <10 % in the more inaccessible routes in rural areas (Tanser et al., 2009). Figure 4.3 shows the overall population-level HIV incidence for men and women for the 2004–2011 period. And Figure 4.4 shows HIV prevalence, incidence and transmission probability by community area in the study area. Previous research has show that between 2000 and 2005 orphanhood doubled. However, in terms of the household impact of HIV/AIDS, no evidence was found for the increase in child-headed or skipped-generation households (Tanser et al., 2008).

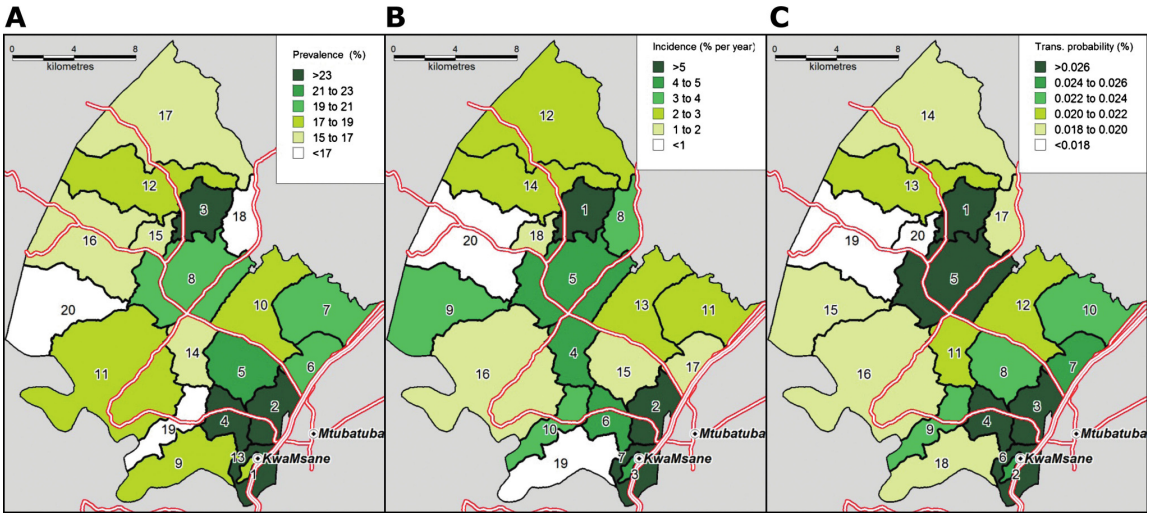

Figure 4.4: Community ranking according to HIV prevalence, incidence, and transmission probability. Each homogeneously colored area is a traditional Zulu community, called an Isigodi. The numbers in the areas represent the community rank according to HIV prevalence (A), incidence (B), and transmission probabilities (C) (Bärnighausen et al., 2010).

4.5 Homesteads, households and residencies

The Africa Centre makes a conceptual distinction between homesteads, households and residencies. Homesteads are are a type of bounded structure. A bounded structure is

defined by the Africa Centre as "a building, or a group of buildings, on land belonging to a single person or organisation, and used for one main purpose" (Africa Center, 2008: 20). These bounded structures are often identified by easily recognizable fences or open land between neighboring homesteads. A homestead is more specifically defined as a grouping of houses or huts on one piece of land, which belongs to a single owner and which is mainly used as a place for people to live (Africa Center, 2008).

	Mean (Low)	Mean (High)
Households per homestead	1.04	1.11
Individuals per homestead	6.65	7.02
Households per individual	1.06	1.07
Individuals per household	6.53	7.22
Household co-members per individual	8.49	9.45

Table 4.1: DSA Household membership and living arrangements. Data are high and low means for the 13 semiannual cross-sections, January 2004-June 2010 (Bor et al., 2011).

The Africa Centre defines households as a "a social group of one or more members [that] share in the joint household resources and know each other well enough to provide information about each other. In each household, one of the members is considered to be the head of household" (Africa Center, 2008: 30). A household member is further defined as a person who considers him or herself as a member of that household, and is considered by household members to be a member. This distinction means that multiple households, which refer mainly to individual memberships, can be contained within a single homestead (a physical dwelling place). In such a scenario, a homestead can begin as a single household with more households established on the same plot of land over time. This could occur when family members separate from the main household to establish their own household on the same plot of land. In another scenario, tenants may move into an existing plot of land and establish their own household.

An individual is a resident of a homestead if he or she physically lives in the homestead. An individual can continue to be a member of a household while they are outside of the study area, but they cannot be recoded as being a resident in the homestead during this time. Table 4.1 shows the data for the homesteads, households, and individuals. There are on average 1.04–1.11 households per homestead. Overall, 8.5–9.5 individuals typically live

within a homestead, and there are on average 6.5–7.2 individuals living within a household. There are additional co-members in a household (8.5–9.5) because individuals can continue to be a household member even through they are not physically present in the household. On average, individuals are members of 1.06–1.07 households. Migration is defined as the event that occurs when an individual or household moves from one homestead to another (Africa Center, 2008). I illustrate residential mobility and external migration concepts in greater detail in Section 5.2.

4.6 Data collection

Subject	Types of information
Homestead	Latitude, longitude, Owner, Number of households.
Household	Formation and dissolution, Household head.
Individuals	Individual details: inc. date of birth, sex, parents. Household membership(s).
Household members	Update household list: members who join, leave or die. Residency status: including pattern of return visits, marital and partnership status, relationship to household head.
Births	Pregnancy outcomes: abortions, still and live births. Delivery environment: including assistance, place, birth-weight.
Deaths	Location and care provision at time of death. Open description of circumstances.
Migrations	Details of place of origin or destination. Type of migration, e.g. household or individual migration.
Child health	On first birthday: vaccination history.

Table 4.2: Data collected at each routine household visit, 2000 and ongoing (Tanser et al., 2008: 958)

4.7 The Hlabisa HIV Treatment and Care Programme

The Hlabisa HIV Treatment and Care Programme was established in late 2004 by the South African Department of Health and the Africa Centre as a response to a national plan which aimed to triple the number of individuals accessing ART between 2007 and 2012. The Hlabisa treatment program has seen a dramatic scale-up of ART since its inception, with

1800 patients on treatment in late 2006 to more than 20,000 by the close of 2012. ART is distributed through 16 primary health care clinics and the local district hospital (Hlabisa) by nurses and treatment counselors using the standard South African drug regimens, which conform to World Health Organization (WHO) ART guidelines. In 2010 patients with CD4 counts$<$ 350 cells/µl were elegible for testing, an increase from the initial treatment eligibility threshold of $<$ 250 cells/µl. Details relating to age, sex, contact information, clinic visits, laboratory data and records of ART activity (WHO clinical stage, previous ART, regimen at initiation, changes to regimen during treatment) are updated and maintained on the ARTemis database (Houlihan et al., 2011). The data from ACDIS can be matched with patient data using each individual's unique South African identification number (Bor et al., 2011).

4.8 Ethical approval

All research initiatives at the Africa Centre are first undertaken in consultation with a Community Advisory Board (CAB) for comment and feedback. The CAB consists of approximately 25 members that are chosen by the community, the Board also provides a forum to discuss the results of specific studies and how best to disseminate these to the community. All data are stored in a secure SQL database on-site; Africa Centre database personnel are responsible for the entering of all data values, coding of all missing values, labelling of all data values, and construction of variables from the raw data. The de-linking of individual names from all records, including all procedures to ensure confidentiality, are undertaken by Africa Centre personnel. All persons in the dataset are anonymous to the investigators. Ethical approval for research conducted by the Africa Centre has been granted by the University of KwaZulu-Natal, South Africa

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Under surveillance at start	88335	90442	90403	90424	90600	90752	91239	93283	92891	93049	93179	93100	93042
Born	2118	2031	2019	1936	2007	2081	2000	2034	2008	1902	1842	1722	1097
Started Membership	1311	563	431	307	291	370	471	410	552	641	918	742	292
Imigrated during year	3033	3087	4346	3227	2585	2455	2370	2318	2038	2283	1927	1358	546
Died during year	1267	1476	1520	1591	1484	1404	1273	1332	1208	1131	1015	934	690
Membership end	1650	1976	2206	1510	1233	1275	1344	1398	1374	1445	1059	399	465
Outmigrated during year	1084	1550	2041	1293	1053	751	582	922	661	739	788	606	318
Lost to follow-up	354	718	1008	900	961	989	1003	1502	1197	1381	1904	1941	1962

Table 4.3: All Individuals (incl. non-residents) at the start of year

Chapter 5

Use of ART in households and risk of HIV acquisition

Background: Studies of HIV-serodiscordant couples in stable sexual relationships have provided convincing evidence that ART can prevent the transmission of HIV. I aimed to quantify the preventive effect of a public sector HIV treatment and care programme based in a community with poor knowledge and disclosure of HIV status, frequent migration, late marriage, and multiple partnerships. Specifically, I assessed whether an individual's hazard of HIV acquisition was associated with ART coverage among household members of the opposite sex.

Methods: In this prospective cohort study, I linked patients' records from a public-sector HIV treatment programme in rural KwaZulu-Natal, South Africa, with population-based HIV surveillance data collected between 2004 and 2012. I used information about coresidence to construct estimates of HIV prevalence and ART coverage for each household. I then regressed the time to HIV seroconversion for 14,505 individuals, who were HIV-uninfected at baseline and individually followed up over time regarding their HIV status, on opposite-sex household ART coverage, controlling for household HIV prevalence and a range of other potential confounders.

Findings: 2037 individual HIV seroconversions were recorded during 54 845 person-years of follow-up. For each increase of ten percentage points in opposite-sex household ART coverage, the HIV acquisition hazard was reduced by 6% (95% CI 2–9), after controlling for other factors. This effect size translates into large reductions in HIV acquisition hazards when household ART coverage is substantially increased. For example, an increase of 50 percentage points in household ART coverage (eg, from 20% to 70%) reduced the hazard of HIV acquisition by 26% (95% CI 9–39).

Interpretation: These findings provide further evidence that ART significantly reduces the risk of onward transmission of HIV in a real-world setting in sub-Saharan Africa.

Awareness that ART can prevent transmission to coresident sexual partners could be a powerful motivator for HIV testing and antiretroviral treatment uptake, retention, and adherence.

5.1 Introduction

Over the past decade, several studies have shown that ART can reduce the transmission of HIV from an infected to an uninfected sexual partner (Baggaley et al., 2013; Anglemyer et al., 2013; Loutfy et al., 2013). The strongest evidence for the preventive effect of ART has come from studies of HIV-serodiscordant couples in stable sexual relationships. In 2011, investigators of the HPTN 052 trial, now regarded as the landmark HIV treatment-as-prevention study, reported that early ART reduced HIV transmission by 96% in HIV-serodiscordant couples who had disclosed their HIV status to each other (Cohen, 2012). This result confirmed the findings of two earlier observational studies, which showed that ART was associated with a 98% (Bunnell et al., 2006) and a 92% (Donnell et al., 2010) reduction in HIV incidence in serodiscordant heterosexual couples. More recently, investigators of a prospective cohort study (He et al., 2013) reported a 66% fall in the rate of new HIV infections among married serodiscordant couples receiving ART. These impressive results have established treatment-as-prevention as an effective strategy to reduce the spread of HIV (Cohen et al., 2013; Montaner, 2011; Hayden, 2010; Cambiano et al., 2011). Attention is now being drawn to whether findings based on the study of serodiscordant couples can be generalized to the broader population (Cohen et al., 2013).

A small number of ecological studies have associated an increase in the uptake of ART with a reduction in the number of new HIV diagnoses for a particular group, community or administrative region over time (Das et al., 2010; Montaner et al., 2010; Wood et al., 2009). However, such studies typically make use of aggregated outcomes and are therefore unable to evaluate the preventive impact of ART at the individual level (Smith et al., 2012). In a recent study, the investigators observed the time to seroconversion for 16,667 HIV-uninfected individuals on the basis of ART coverage in the local surrounding community (Tanser et al., 2013). They defined ART coverage as the proportion of all HIV-infected people on ART irrespective of CD4 count or disease stage. After controlling for multiple determinants, they found that an individual living in a community with 30% ART coverage

was 38% less likely to acquire HIV relative to an individual living in a community with low ART coverage (<10% of all HIV-infected individuals on ART). This result provided powerful evidence for the community-level effectiveness of treatment as prevention. However, no previous study has assessed the preventive effect of ART at the household level.

Here, I aim to quantify the household-level preventive effect of a public-sector HIV treatment and care programme based in a rural South African community with poor knowledge and disclosure of HIV status, frequent migration, late marriage, and multiple partnerships. Specifically, I use information about the HIV serostatus and ART status of household residents to assess whether ART is associated with a reduction in HIV acquisition risk.

5.2 Methods

5.2.1 Study population

The Africa Centre's population-based surveillance, which was designed to mirror the demographic reality of a highly fluid and complex community, is located in the uMkanyakude district of the northern KwaZulu-Natal province. The study area is approximately 440 km^2 in size with a resident population of 75,000 and a total (resident and non-resident) population of 87,000 at any given time-point. The area is generally poor and typical of a rural South African population, with scattered, informal peri-urban settlements and a principal urban township (Tanser et al., 2008). The level of unemployment is very high, with around 66% of working-age adults without work (Bor et al., 2012). Approximately 62% of the population have access to electricity and 78% access to piped water (not necessarily within their household) (Tanser et al., 2008).

The study area is characterized by high levels of individual mobility and a dynamic household structure, two social conditions which have their origin in the Apartheid-era. From the 1950s until the democratic transition in 1994, Apartheid authorities set about redrawing the South African landscape along racial lines as a means to consolidate white rule (Mamdani, 1996). This form of social engineering saw the development of white urban centers and cities and the resettlement of black Africans into underdeveloped homelands or rural areas. Racial segregation and resettlement was largely seen as the vehicle for "a more 'rational' distribution of African labor between the urban areas and white farms"

(Posel, 1993). The study area, which now includes land under the Zulu tribal authority, was formerly part of the homeland system of the Bantu Authorities Act of 1951 (Crankshaw, 2002).

The migrant labor system under Apartheid was further entrenched with the 1952 Pass Laws Act (in effect until 1986), which prohibited African adults from staying in white urban areas without employment or accommodation. If working in urban centers, African laborers were required to reside in segregated single-sex hostels and were prevented from being joined by their partners or families. The extended absence of men from the rural family home, the migration of both men and women, and separated living spheres led to prolonged physical separation and marital instability during this period (Hosegood et al., 2009; Preston-Whyte, 1993; Murray, 1981).

The control of settlement, together with the migrant labor system and the lack of local employment opportunities, has resulted in high levels of mobility and migration within the study area at present. Female-headed households are typical, and are largely the product of male out-migration to urban areas in search of employment and income. Research conducted here previously shows that 23% of all household members reside elsewhere; and that approximately 35% of adult (18 years or older) female household members and 40% of adult males reside outside the area but return periodically and maintain memberships with households (Hosegood et al., 2004, 2007). Research has also shown a high level of household mobility, with 11% of the households moving at least once during the 2.5 years of the study (Hosegood et al., 2004).

Partnership stability in the study area has also been profoundly affected by the impact of frequent and long-term migration. More recently, marital rates (an important indicator of partnership stability) have been on the decline for adults since 2000; in 2006, less than 20% of women and 10% of men aged 35 years or younger in our study area were ever married (Hosegood et al., 2009). Polygamous marriages constituted 12% of all marriages in women and 14% in men in 2006, higher than the national estimate of 7% at that time (Hosegood et al., 2009). If it occurs, marriage is typically late for a male (median 34 years) (Statistics South Africa, 2012) once he is able to afford the Zulu bridewealth payment: during this time he may have had several casual relationships, and increased his or his sexual partner's risk of HIV infection (Ott et al., 2011; Hosegood et al., 2009). Among men who were sexually

active, 28.9% (95% CI 27.0–30.8) reported having two or more concurrent partners, and the median number of reported lifetime partners was five (Interquartile Range 3–8) (Tanser et al., 2011). The mean number of reported lifetime sexual partners (6.3) varied between 3.4 and 12.9 in communities across the surveillance area between 2004 and 2009 (Tanser et al., 2011; Todd et al., 2009).

The population-based HIV incidence between 2004 and 2010 was 2.63 new infections per 100 person-years (95% CI 2.50 to 2.77) (Tanser et al., 2013). Incidence peaked at 6.6 per 100 person-years in women at age 24, and 5 years later in men at 4.1 per 100 person-years of observation (Tanser et al., 2013). There has been a steady increase in HIV prevalence from 21.8% (95% CI 20.9–22.7) in 2004 to 29.0% (95% CI 27.9–30.1) in 2011 for the 15 to 49 age-group (Zaidi et al., 2013). ART was made available to patients with CD4+ counts <200 cells/µl through government primary health-care clinics in September 2004. In April 2010, treatment eligibility was increased to <350 cells/µl for pregnant women and tuberculosis patients and then for all adults in August 2011, using the standard South African eligibility criteria and World Health Organisation (WHO) treatment guidelines (Lessells et al., 2013). ART coverage estimates have risen sharply from 0.0% (95% CI 0.0–0.2) in 2004 to 30.7% (95% CI 29.3–32.1) in 2011; with 40% and 30% of all HIV-infected women and men aged 25 to 49 years having successfully initiated ART (Zaidi et al., 2013).

The Africa Centre collects data on individuals who are members of one or more family units or households. I define a household as a building or a group of buildings belonging to a single owner and used by residents for the purposes of living (Africa Center, 2008). The average size of a household is seven resident members (Bor et al., 2011). Approximately 21,500 households have been included in the Africa Centre household surveillance since 2000. Household response rates are typically >95%, and information is collected on both resident and non-resident members. Individual HIV testing has taken place within the household surveillance on an annual basis since 2003. Eligible participants aged ≥15 years are interviewed in private by trained field workers, who extract blood by finger prick for HIV testing. About 80% of all individuals consent to provide a blood sample for anonymous HIV testing (Tanser et al., 2008). ART is distributed through the HIV Treatment and Care Programme by nurses and treatment counselors, and records of patient HIV serostatus and ART status are updated and maintained in the ART Evaluation and Monitoring System

(ARTemis) database (Houlihan et al., 2011). The Africa Centre surveillance and HIV treatment programme are described in greater detail in Section 4.7.

5.2.2 Outcome and exposure measures

Seroconversion Event: The outcome measure of this study is the time to seroconversion for a repeat-tester. I define a repeat-tester as an individual, aged 15 to 50 years, who 1) has had more than one HIV test, 2) was HIV-uninfected at first test, and 3) was a resident member of at least one household in the surveillance area between January 2004 and December 2012. These 18,802 repeat-testers, who are at risk of HIV infection, are a subset of the total resident population under surveillance. I excluded 6270 households that did not have a repeat-tester as a resident, as these households were unrelated to the study outcome.

A seroconversion event is defined as the point at which the repeat-tester tests positive for HIV antibodies in the blood. The precise time at which a seroconversion event occurs is difficult to establish in the absence of regular HIV testing. In this analysis, the seroconversion event was determined by taking the mid-point of a repeat-tester's latest HIV-negative (lower bound) and earliest HIV-positive (upper bound) test date. Figure 5.1 shows an example for a repeat-tester, whose latest HIV-negative and earliest HIV-positive status was observed on 15 May 2008 and 22 November 2008 respectively. The mid-point of this interval, 18 August 2008, is the inferred seroconversion date. I right-censored the data for repeat-testers who were HIV-uninfected at their last clinic visit date, who were lost to follow-up, or who migrated out of the surveillance area.

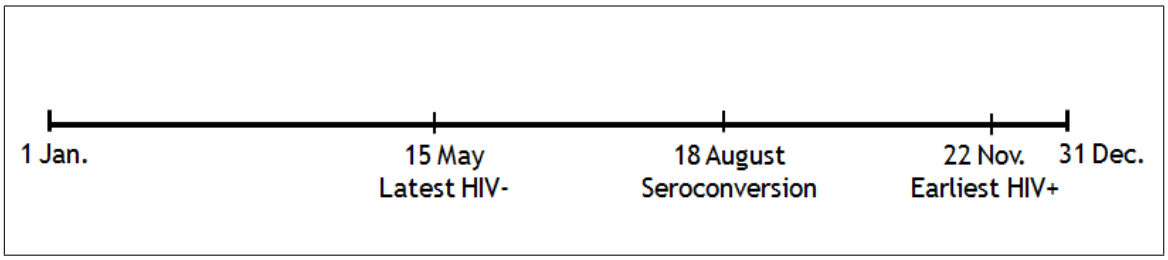

Figure 5.1: Computation of a repeat-tester's seroconversion date: an example

Exposure Episodes: I used an exposure episode to measure the number of days spent by a repeat-tester in a single, distinct household within a calendar year, and to enumerate the co-resident characteristics of the household for the corresponding exposure episode. Changes in household residencies within the surveillance area were captured with each new exposure episode.

The household surveillance captures the complexity of a repeat-tester's living arrangements through exposure episodes. The exposure episodes concept is built into the design of the Africa Centre data so as to capture the complex life-cycle of the household and its residents. The first timeline in Figure 5.2 shows an example of a single exposure episode, which can span no more than the length of calendar year. Typically, two episodes per year are created for a repeat-tester: the length of the first episode is from the 1st of January until his or her birthday, and the length of the second episode is from his or her birthday to the 31st of December. The second timeline in Figure 5.2 shows an example of repeat-tester born on June 27th, 1981: here, the duration of the first episode would be 178 days and the second episode 187 days.

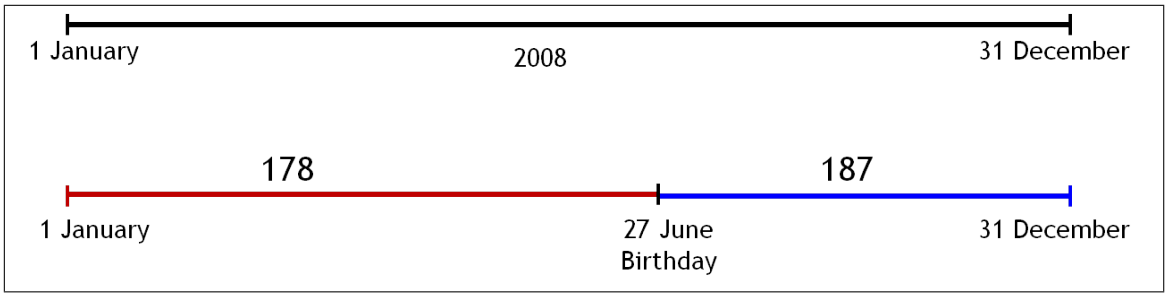

Figure 5.2: Example showing a single exposure episode (top timeline) for a calender year (e.g., 2008) and the bifurcation of the calender into two exposure episodes by birthdate (bottom timeline)

Importantly, additional and separate episodes are created for a calender year when a change in a repeat-tester's residency status is observed. A new exposure episode begins with the start of a new household residency; and ends with the migration of the repeat-tester to a different household within (or outside) the surveillance area. Figure 5.3 shows a simple example of how new exposure episodes are created when the repeat-tester migrates out of the household (or returns to it). The first episode begins for a resident repeat-tester on the

1st of January. On May 20th, the repeat-tester migrates out of the household and returns December 1st. This change in residential residency creates a two episodes in addition to the episodes created by the birthday bifurcation, giving four exposure episodes in total for the 2008 calender year. The exposure episode in the first household sums to 140 days; the next two episodes outside of the first household sum to 195 days; and the duration of the fourth episode is 30 days.

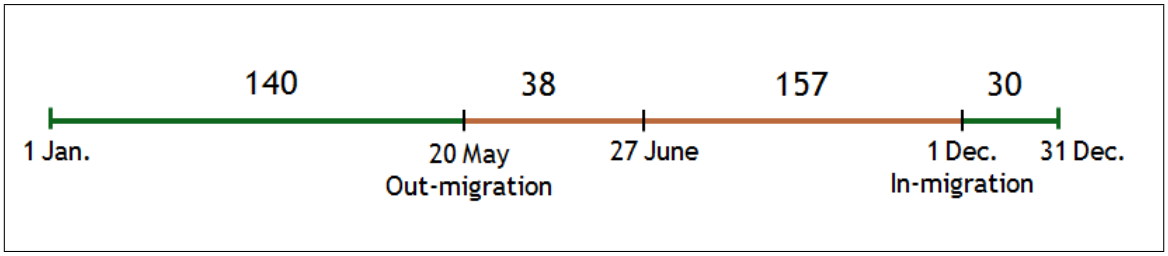

Figure 5.3: Residential mobility and the computation of household exposure episodes (in days) for the calender year (2008): an example

To continue the example, consider that the repeat-tester belongs to household number 1116 on 1 January 2008. The data indicates that there was at least one HIV-infected resident member in this household until the outmigration of the repeat-tester on May 20th. The repeat-tester migrates to household 214, where there is at least one resident observed to be on ART. The repeat-tester returns to household 1116 on the 20th of December, where records indicate that there is still one or more HIV-infected coresidents physically living in this household. With this information, the exposure time for each household for the 2008 calender year can be calculated as follows: the repeat-tester spends two episodes and 170 (140 + 30) days in household number 1116 with $\geq$ 1 HIV-infected resident(s), and two episodes and 195 (38 + 157) days in household number 214 with $\geq$ 1 resident(s) on ART. It is with this method that a repeat-tester's exposure time to HIV and ART within different households is computed.

Co-resident characteristics: I am interested in a repeat-tester's time to HIV seroconversion for varying levels of ART coverage and HIV prevalence in the household. To do this

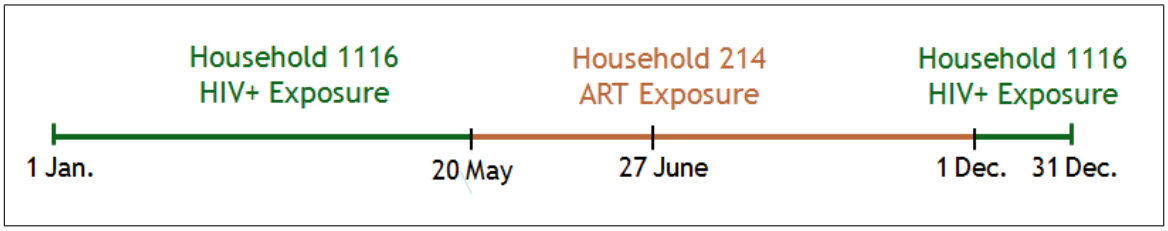

Figure 5.4: Calculation of exposure time to households with varying HIV prevalence and ART coverage for a calender year: an example

I individually linked 7657 adults enrolled in the local HIV treatment and care programme—who successfully initiated ART and had an active follow-up status—with the same individuals in the surveillance database. I used the linked records to determine if a co-resident was 1) HIV-infected and not on ART, 2) HIV-infected and on ART, or 3) HIV-uninfected at any given time-point. I then used the information of each co-resident's HIV serostatus and ART treatment status to construct an HIV prevalence and an ART coverage measure for the corresponding household. I define HIV prevalence as the total number of co-residents (denominator) who are HIV-infected (numerator), and ART coverage as the total number of HIV-infected co-residents (denominator) who are on ART (numerator). The household ART coverage measure includes information on co-residents who are HIV-infected but not on treatment.

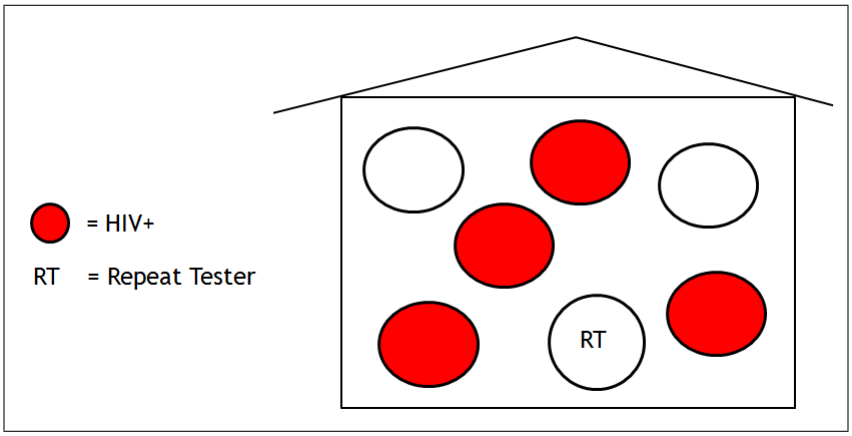

Figure 5.5: Example for the computation of household HIV prevalence

Figure 5.5 shows an example of how the HIV prevalence measure is computed for each household. The circles in the household represent each coresident ($n = 7$), and the shaded areas represent coresident members who are HIV-infected ($n = 4$). The HIV prevalence for this household is 66%, with the repeat-tester being excluded from the denominator of this calculation (the repeat-tester cannot be at-risk *and* an exposure unto him/herself). Figure 5.6 shows how the ART coverage measure is computed for the same household. One of the four HIV-infected coresidents is on treatment, giving an ART coverage of 25% for this household.

In our study, I use the household as a proxy for co-resident partners of the repeat-tester. The household is a proxy because I do not specifically identify if the repeat-tester is in a sexual relationship with one or more co-residents for a given exposure episode. In order to construct reasonable ART coverage and HIV prevalence measures, I excluded co-resident members younger than 15 years of age and within a 15 year age-gap of the repeat-tester to prevent family members—grandparents, parents or children—of the repeat-tester from being considered as possible sexual partners in the household. To ensure sufficient exposure to HIV-infected co-residents (who are either on ART or not), I excluded 4297 repeat-testers from our analysis with >50% non-residency exposure episodes. In addition, I excluded the repeat-tester from the denominator of his or her HIV prevalence measure, and therefore did not obtain a prevalence measure for single-person households in which the repeat-tester was the only resident. Importantly, I used detailed surveillance information on co-resident deaths, out-migrations, and loss to follow-up to dynamically update the respective numerator or denominator of the household ART coverage and HIV prevalence measures for each exposure episode accumulated by the repeat-tester.

It is likely that a reduction in HIV acquisition risk could be confounded with the unobserved behaviors of the household residents. These behaviors, which may involve routine HIV screening, regular health-care visits, the use of condoms, risk-adverse sexual practices, abstinence, and fidelity, for example, could account for a reduction in HIV transmission risk independently of ART. Failure to consider these 'health-seeking' behaviors as a source of confounding could lead to an over-estimation of the biological impact of ART on the risk of HIV acquisition. I undertook the following measures to address this problem.

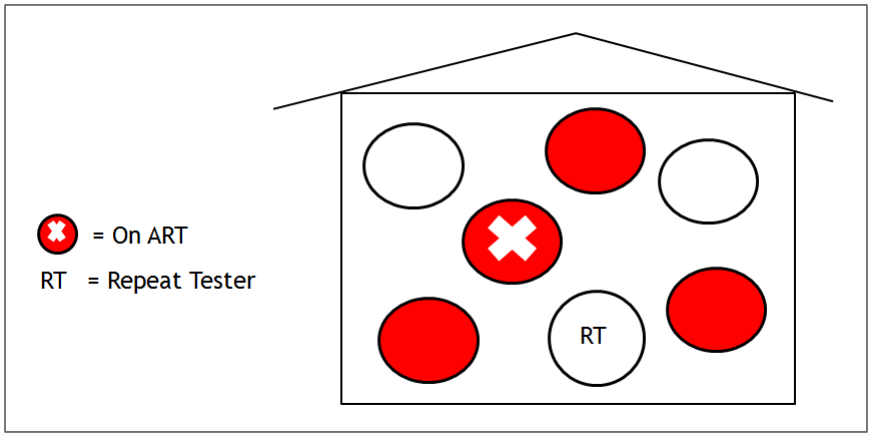

Figure 5.6: Example for the computation of household ART coverage

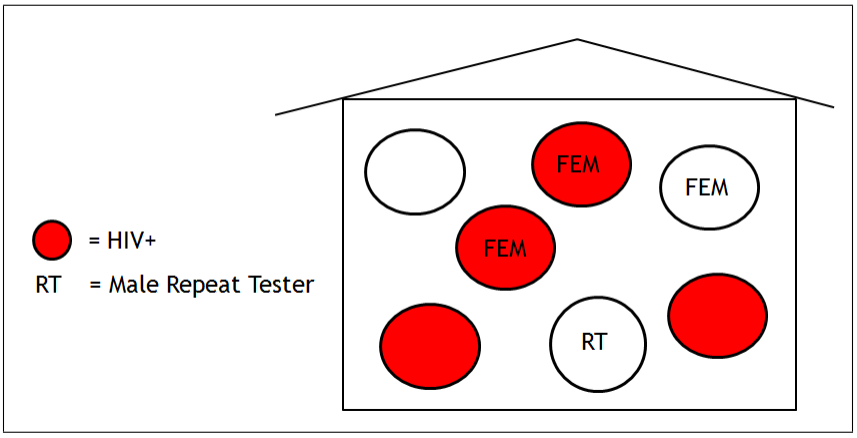

Figure 5.7: Example for the computation of sex-directional HIV prevalence in the household

Given the heterosexual transmission of HIV in our study area (Tanser et al., 2011), I acknowledged that ART would have a preventive benefit for partners of the opposite-sex. I constructed two ART coverage measures for the household, each based on co-resident sex; and repeated this exercise for the household HIV prevalence measure. I hypothesized that a female repeat-tester's HIV acquisition risk would be a function of the opposite-sex (male)—but not the same-sex (female)—ART coverage level in the household, and similarly for a male repeat-tester. A significant decline in HIV acquisition risk associated with an increase in opposite-sex household ART usage would support the treatment-as-prevention hypothesis at the biological (heterosexual) level. A decline in HIV acquisition risk would

not be associated with both the opposite-sex ART *and* same-sex coverage measures: this scenario would indicate confounding of the preventive effect of ART with the unobserved 'health-seeking' behaviors of the household.

Figure 5.7 shows an example of how sex-directional HIV prevalence is computed for each household. In this example, the repeat-tester is a male resident, and three of the co-residents are female (the circles now contain a "FEM" indicator). Of these three females, two are HIV-infected, which gives a 66% opposite-sex HIV prevalence for this household. Figure 5.8 shows that one of the two HIV-infected female co-residents is on ART, which gives an opposite-sex ART coverage of 50% for this household.

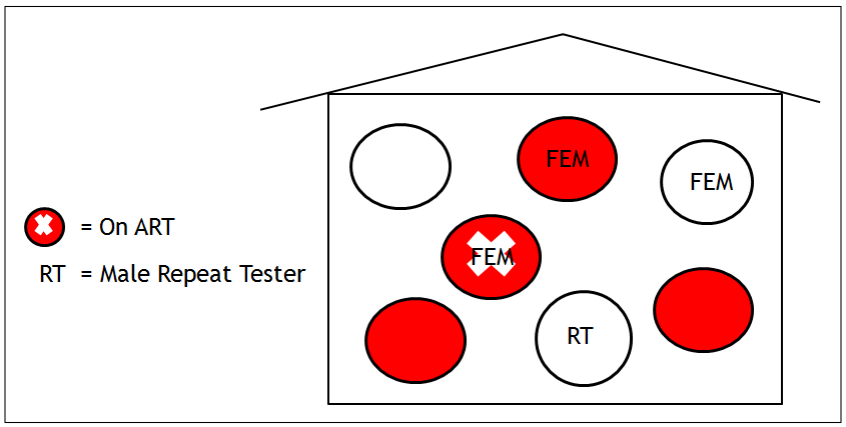

Figure 5.8: Example for the computation of sex-directional ART coverage in the household

5.2.3 Data analysis

I used a Cox proportional hazards model to obtain an estimate for a repeat-tester's hazard of seroconverting conditional on household ART coverage, and adjusting for household HIV prevalence, age and sex, awareness of HIV status and ART (yes, no, refused), area of residence (rural, peri-urban, urban), household socio-economic status (in 20-quantiles), number of opposite-sex household residents, and the number of household residency changes by the repeat-tester (none, one, or two or more). All variables apart from the repeat-tester's sex were time-varying. I report 95% CIs based on standard errors that have been adjusted for clustering at the household level.

The main results are reported for a regression model based on data for opposite-sex coresidents only (opposite-sex model). Even after controlling for the independent variables in the opposite-sex regression model, the relation between HIV seroconversion hazard and household opposite-sex ART coverage could be confounded by a range of unobserved factors, such as conscientiousness of individual household members, attitudes towards risk, and attitudes towards health. Although I cannot include these factors in the regression because I do not have data for them, I can control for their confounding effects by adding same-sex ART coverage and same-sex HIV prevalence. A household's same-sex ART coverage will depend on many of the same unobserved factors, such as household members' conscientiousness and attitudes, that are also likely to affect a household's opposite-sex ART coverage. Thus I also report the results after adding household same-sex ART coverage and same-sex HIV prevalence to the regression (full model). I also did an alternative analysis in which household ART coverage and HIV prevalence were treated as binary variables (none vs one or more HIV-infected coresidents on ART, and none vs one or more HIV-infected coresidents) rather than in units of ten percentage points.

5.2.4 Statistical model

Survival models differ from standard regression models in their ability to account for the censoring or the truncation of data (Gutierrez, 2002). The survival function, $S(t)$, gives the probability that a person survives longer than some specified time. The hazard function, $h(t)$, gives the instantaneous potential per unit time for the event to occur, given that the individual has survived up to time t. The hazard function focuses on the person failing or the event occurring. The hazard rate is expressed as:

$$h(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T \leq t + \Delta t | T \geq t)}{\Delta t} \tag{5.1}$$

This definition gives the probability that a person's survival time will lie between the interval t and $t + \Delta t$ given that the survival time is greater or equal to t (Kleinbaum and Klein, 2005). The measure of effect is a hazard ratio, which is the exponential of one or more regression coefficients in the model. The interpretation of a hazard ratio (HR) is much like an odds ratio. Cox proportional hazard models are typically used to undertake survival

analysis. The formula is written in terms of the hazard function, which is:

$$h(t) = h_0(t)\, exp\left(\sum_{i=1}^{p} \beta_i X_i\right)$$

where $\mathbf{X}$ is a vector of predictor variables. The Cox formula states that the hazard at time t is the product of the baseline hazard function $h(t)$ and the exponent of the linear expression $\beta_i X_i$ over the explanatory variables $\mathbf{X}$ (Kleinbaum and Klein, 2005). This is a time independent model since the second term does not involve t. The hazard ratio is obtained by dividing the hazard for one individual or a group by the hazard for a different individual or group. The HR is obtained, using the maximum likelihood approach, with:

$$\widehat{\text{HR}} = \frac{\hat{h}(t, \mathbf{X})}{\hat{h}(t, \mathbf{X}^*)} = \frac{h_0(t)\, exp^{\left(\sum_{i=1}^{p} \hat{\beta}_i X_i\right)}}{h_0(t)\, exp^{\left(\sum_{i=1}^{p} \hat{\beta}_i X_i^*\right)}} = exp\left(\sum_{i=1}^{p} \hat{\beta}_i (X_i - X_i^*)\right)$$

where $\mathbf{X}^*$ denotes the set of predictors for a treatment individual or group, and $\mathbf{X}$ for a control or placebo group. Extended Cox models include variables that are time-dependent. A time-dependent variable is defined as any variable whose value for a given subject may vary over time (Kleinbaum and Klein, 2005). An extended Cox model can be written as:

$$h(t, \mathbf{X}(t)) = h_0(t)\, \exp\left[\sum_{i=1}^{p1} \hat{\beta}_i X_i + \sum_{i=1}^{p2} \delta_j X_j(t)\right]$$

where $X_1(t), X_2(t), \ldots X_{p2}(t)$ are defined as the time-independent variables. The hazard ratio is now defined as:

$$\widehat{\text{HR}} = \frac{\hat{h}(t, \mathbf{X}(t))}{\hat{h}(t, \mathbf{X}^*(t))} = \exp\left[\sum_{i=1}^{p1} \hat{\beta}_i [X_i - X_i^*] + \sum_{i=1}^{p2} \delta_j [X_j(t) - X_j^*(t)]\right]$$

$\mathbf{X}^*(t)$ and $\mathbf{X}(t)$ are two sets of predictors that identify two specifications at time t for time-dependent and time-independent variables.

5.3 Results

14,505 repeat-testers met the inclusion and exclusion criteria of whom 8546 (59%) were women. 2037 HIV seroconversions were recorded over 54,845 person-years of follow-up

time during the 2004–12 period. The median follow-up time per repeat-tester was 3.2 years (IQR 1.8–5.5), with a maximum of 10.2 years. The unadjusted HIV incidence over the study period was 3.7 new infections per 100 person-years (95% CI 3.6–3.9). Incidence was highest in the 20–24 years age group for women and in the 25–29 years age group for men (Table 5.2). Unadjusted HIV incidence remained stable from 2004 to 2008 and then fell from 3.9 per 100 person-years in 2008 to 2.8 per 100 person-years in 2012 (Table 5.2). An average of 4102 (range 1131–5119) households per year were included in the analysis during the study period. About 10% of the repeat-testers changed household residencies one or more times during the study period. Repeat-testers were exposed to a mean of 1.2 (SD 0.5) different ART coverage levels (coded in units of ten percentage points). Figures 5.9 and 5.10 show the change in mean HIV prevalence and ART coverage in the household over time.

	Adjusted HR	**95% CI**
10 percentage points	0.94	0.91–0.98
20 percentage points	0.89	0.82–0.96
30 percentage points	0.84	0.74–0.94
40 percentage points	0.79	0.67–0.92
50 percentage points	0.74	0.61–0.91
60 percentage points	0.70	0.55–0.89
70 percentage points	0.66	0.50–0.87
80 percentage points	0.62	0.45–0.85
90 percentage points	0.58	0.41–0.84
100 percentage points	0.55	0.37–0.82

Table 5.1: Effect of percentage-point increases in opposite-sex household ART coverage on HIV acquisition hazard

For every increase of ten percentage points in opposite-sex household ART coverage the hazard of HIV acquisition was reduced by 6% (95% CI 2–9), after controlling for household HIV prevalence and the other independent variables (Table 5.3).[1] Table 5.1 shows the adjusted HIV acquisition hazards for different percentage point increases in household ART

[1] In Table 5.3, 95% CIs are based on SEs that have been adjusted for clustering at the household level.
[a] Adjusted hazard ratio represents the change in HIV seroconversion hazard for any increase of ten percentage points in household ART coverage, controlling for the other independent variables in the regression model.
[b] Adjusted hazard ratio represents the change in HIV seroconversion hazard for any increase of ten percentage points in household HIV prevalence, controlling for the other independent variables in the regression model.

coverage.[2] For example, an increase of 50 percentage points in opposite-sex household ART coverage (eg, an increase from 0% to 50%, from 10% to 60%, or from 20% to 70%), was associated with a 26% (95% CI 9–39) reduction in the hazard of HIV acquisition.

The full model included measures of same-sex ART coverage and same-sex HIV prevalence. The point estimate for the change in hazard of HIV acquisition for an increase of ten percentage points in household ART coverage was the same as the one in the opposite-sex model (Table 5.3). The adjusted hazard ratio (HR) for household same-sex HIV prevalence was not significant (Table 5.3), implying that the opposite-sex ART coverage hazard ratios are not being confounded with the unobserved 'health-seeking' behaviors of the household.

[2] Data in Table 5.1 are adjusted for opposite-sex household HIV prevalence and the other independent variables included in the opposite-sex model; the effect size for each percentage-point increase will be the same irrespective of the baseline coverage.

Variable	Person-years	No. Seroconversions	Rate/100 person-years	95% CI
Calender year				
2004	5,552	208	3.75	3.27–4.29
2005	7,060	269	3.81	3.38–4.29
2006	7,575	321	4.24	3.80–4.73
2007	7,347	268	3.65	3.24–4.11
2008	7,102	275	3.87	3.44–4.36
2009	6,389	237	3.71	3.27–4.21
2010	5,724	203	3.55	3.09–4.07
2011	4,858	164	3.38	2.90–3.93
2012	3,239	92	2.84	2.32–3.48
Age-Sex Strata				
Female 15–19	9,179	451	4.91	4.48–5.39
Female 20–24	7,478	583	7.80	7.19–8.46
Female 25–29	3,140	204	6.50	5.66–7.45
Female 30–34	2,271	96	4.23	3.46–5.16
Female 35–39	2,795	70	2.50	1.98–3.17
Female 40–44	3,513	77	2.19	1.75–2.74
Female 45–50	5,349	73	1.36	1.09–1.72
Male 15–19	8,373	75	0.90	0.71–1.12
Male 20–24	5,848	192	3.28	2.85–3.78
Male 25–29	2,082	97	4.66	3.82–5.68
Male 30–34	1,171	38	3.25	2.36–4.46
Male 35–39	1,039	31	2.98	2.10–4.24
Male 40–44	1,076	24	2.23	1.50–3.33
Male 45–50	1,531	26	1.70	1.16–2.49
Knows HIV Status				
No	36,596	1,372	3.75	3.56–3.95
Refused	4,331	131	3.02	2.55–3.59
Yes	13,918	534	3.84	3.52–4.18
Heard about ART				
No	23,614	880	3.73	3.49–3.98
Refused	4,452	134	3.01	2.54–3.56
Yes	26,778	1,023	3.82	3.59–4.06
Area				
Peri-urban	16,597	724	4.36	4.06–4.69
Rural	36,613	1,248	3.41	3.22–3.60
Urban	1,634	65	3.98	3.12–5.07
Household wealth quintile				
Poorest	11,155	364	3.26	2.94–3.62
2nd poorest	12,254	439	3.58	3.26–3.93
3rd poorest	11,861	464	3.91	3.57–4.28
4th poorest	10,994	473	4.30	3.93–4.71
Wealthiest	8,582	297	3.46	3.09–3.88
No. of household changes				
None	50,481	1,828	3.62	3.46–3.79
Once	3,642	169	4.64	3.99–5.39
More than once	722	40	5.54	4.06–7.55

Table 5.2: Incidence of HIV-1 seroconversion by sociodemographic variables, 2004–12

	(1) Opposite-sex Model			(2) Same-sex Model		
	HR	**(CI)**	**p-value**	**HR**	**(CI)**	**p-value**
Household ART coverage[a]						
Opposite-sex	0.9424	(0.9055–0.9808)	0.004	0.9421	(0.9052–0.9805)	0.003
Household HIV prevalence[b]						
Opposite-sex	1.0509	(1.0309–1.0713)	<0.001	1.0508	(1.0309–1.0712)	<0.001
No. of household residents:						
Opposite-sex	0.9862	(0.9555–1.0178)	0.387	0.9834	(0.9522–1.0157)	0.311
Knows HIV status:						
Yes	1			1		
No	1.1136	(0.9912–1.2511)	0.070	1.1141	(0.9916–1.2516)	0.069
Refused	1.3032	(0.6052–2.8064)	0.499	1.2997	(0.6052–2.7915)	0.501
Heard about ART:						
Yes	1			1		
No	0.9817	(0.8782–1.0974)	0.745	0.9844	(0.8805–1.1006)	0.783
Refused	0.7019	(0.3298–1.4934)	0.358	0.7046	(0.3320–1.4953)	0.362
Age-Sex strata:						
Male 15–19	1			1		
Male 20–24	3.7643	(2.8720–4.9337)	<0.001	3.7687	(2.8752–4.9397)	<0.001
Male 25–29	5.3562	(3.9508–7.2616)	<0.001	5.3564	(3.9493–7.2649)	<0.001
Male 30–34	3.7199	(2.4745–5.5922)	<0.001	3.7025	(2.4644–5.5626)	<0.001
Male 35–39	3.3880	(2.2332–5.1401)	<0.001	3.3760	(2.2280–5.1156)	<0.001
Male 40–44	2.5681	(1.6200–4.0710)	<0.001	2.5596	(1.6142–4.0587)	<0.001
Male $\geq$ 45	2.0097	(1.2819–3.1507)	0.002	2.0059	(1.2796–3.1444)	0.002
Female 15–19	5.7546	(4.5210–7.3248)	<0.001	5.7475	(4.5119–7.3215)	<0.001
Female 20–24	9.5938	(7.5211–12.2375)	<0.001	9.5838	(7.5067–12.2357)	<0.001
Female 25-29	8.0424	(6.1459–10.5242)	<0.001	8.0380	(6.1384–10.5255)	<0.001
Female 30–34	5.1052	(3.7801–6.8948)	<0.001	5.0973	(3.7701–6.8918)	<0.001
Female 35–39	3.0302	(2.1765–4.2186)	<0.001	3.0257	(2.1714–4.2161)	<0.001
Female 40–44	2.6354	(1.9025–3.6505)	<0.001	2.6340	(1.9004–3.6507)	<0.001
Female $\geq$ 45	1.6802	(1.2127–2.3280)	0.002	1.6802	(1.2121–2.3290)	0.002
Area of residence:						
Rural	1			1		
Peri-urban	1.2844	(1.1554–1.4278)	<0.001	1.2836	(1.1548–1.4268)	<0.001
Urban	1.2544	(0.9528–1.6513)	0.106	1.2538	(0.9525–1.6505)	0.107
Household wealth quintile:						
Poorest	1			1		
2nd poorest	1.0535	(0.9146–1.2136)	0.470	1.0536	(0.9146–1.2138)	0.469
3rd poorest	1.0822	(0.9351–1.2524)	0.289	1.0814	(0.9344–1.2515)	0.294
4th poorest	1.1571	(0.9965–1.3436)	0.056	1.1567	(0.9962–1.3431)	0.056
Wealthiest	0.9374	(0.7874–1.1161)	0.468	0.9369	(0.7870–1.1153)	0.464
No. of household changes:						
None	1			1		
Once	1.1469	(0.9716–1.3537)	0.105	1.1459	(0.9708–1.3527)	0.108
Twice or more	1.2650	(0.9239–1.7320)	0.143	1.2653	(0.9242–1.7324)	0.142
Household ART coverage[a]						
Same-sex				1.0267	(0.9780–1.0779)	0.288
Household HIV prevalence[b]						
Same-sex				1.0048	(0.9588–1.0529)	0.843
Seroconversions N	2,037			2,037		
At-risk Individuals N	14,505			14,505		
Exposure Episodes N	118,032			118,032		

Hazard ratio (HR), Confidence interval (CI). Standard errors adjusted for household clusters.

Table 5.3: Results of multivariable analysis for the effect of an increase in opposite-sex household ART coverage on HIV seroconversion hazard

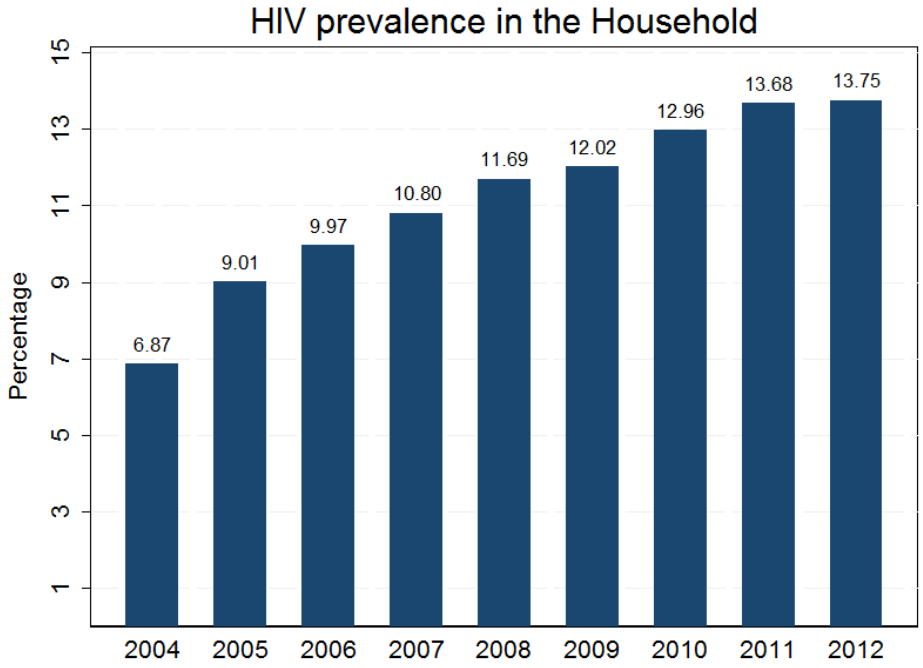

Figure 5.9: Mean HIV prevalence by household: 2004–2012

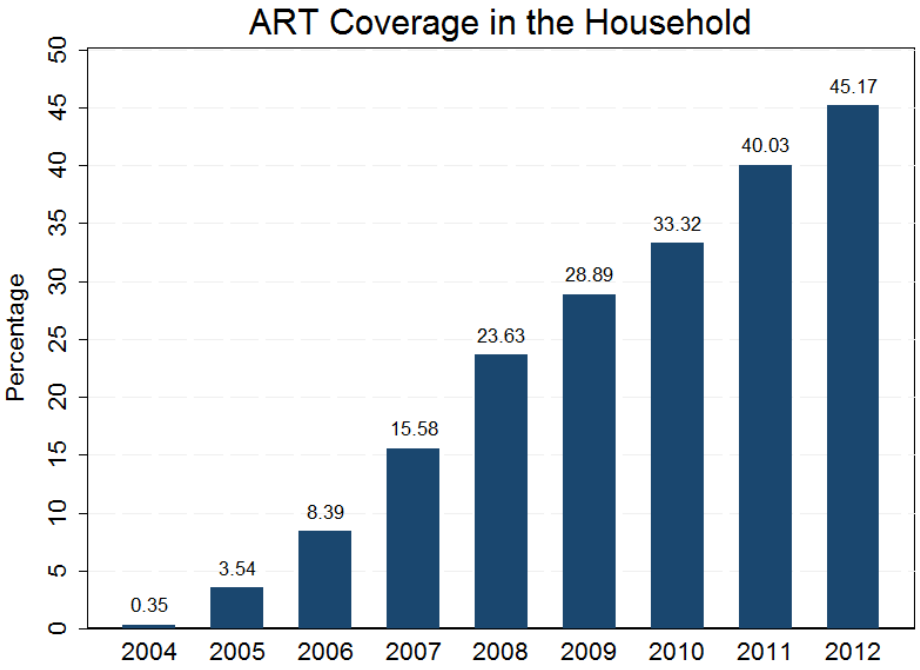

Figure 5.10: Mean ART coverage by household: 2004–2012

Alternative analysis: In this section I undertake an alternative analysis of the preventive benefits of ART. Rather than quantifying the ART coverage and HIV prevalence measures for each household, I consider a repeat-tester to be a resident of one of four types of households, which have:

1. one or more HIV-infected co-resident(s);
2. one or more opposite-sex co-resident(s) who are HIV-infected and on ART;
3. each opposite-sex co-resident is HIV-uninfected;
4. the HIV status of each opposite-sex co-resident is unknown (Figure 5.11).

The four types of households present an alternative method for quantifying the repeat-tester's exposure to ART. Here, the comparison is between household types, rather than the affect of ART coverage and HIV prevalence levels within the household, on a repeat-tester's risk of HIV acquisition. I undertake this analysis to ensure that the results produced in the main analysis are not an artifact of the conceptual design—the decision to compute ART coverage and HIV prevalence measures for each household.

Table 5.4 gives descriptive statistics of the household and HIV/ART-related characteristics by calender year. Table 5.5 shows the results for the opposite-sex and same-sex household types. In the alternative analysis, the hazard of HIV acquisition for an individual living in a household with at least one HIV-infected coresident on ART was 23% less than for an individual living in a household in which none of the HIV-infected coresidents were on ART (adjusted HR 0.77, 95% CI 0.63–0.94, p=0.011).

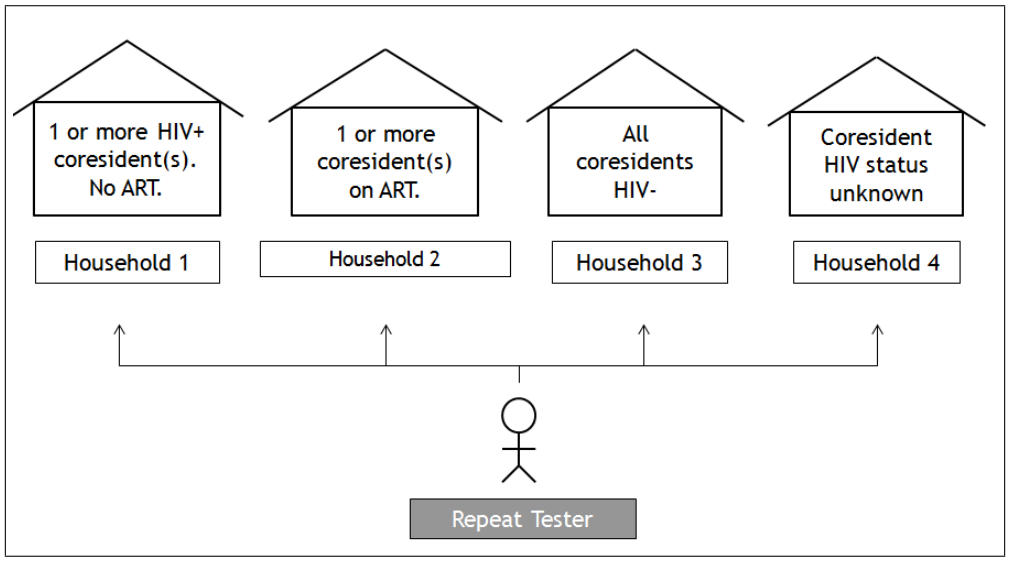

Figure 5.11: Schema for household HIV and ART measures in the alternative analysis

	2004	2005	2006	2007	2008	2009	2010	2011	2012
Household count	11,254	11,328	12,287	12,361	12,419	12,511	12,525	12,365	11,962
Inidvidual residents per household	9.53	9.41	9.19	9.18	9.18	9.2	9.17	9.16	9.08
Household count with a HIV+ coresident	2,415	2,986	3,410	3,829	4,176	4,544	5,037	5,202	5,227
Percentage of these households	21.46	26.36	27.75	30.98	33.63	36.32	40.22	42.07	43.7
Household count with a coresident on ART	4	107	304	567	928	1,244	1,608	1,965	2,075
Percentage of these household	.04	.94	2.47	4.59	7.47	9.94	12.84	15.89	17.35

Table 5.4: Households with HIV+ residents and residents on ART in the study area

	Alternative Model		
	HR	**(CI)**	**p-value**
Homestead Exposure:			
≥1 HIV+ co-resident(s)	1		
All co-residents known HIV−	0.5713	(0.3901–0.8366)	0.004
Co-resident HIV status unknown	0.8809	(0.7822–0.9921)	0.037
≥ 1 co-resident(s) on ART	0.7717	(0.6319–0.9425)	0.011
Heard about ART:			
Yes	1		
No	1.2879	(1.1621–1.4274)	<0.001
Refused	0.9174	(0.3612–2.3302)	0.856
Knows HIV status:			
Yes	1		
No	0.7544	(0.6758–0.8422)	<0.001
Refused	0.9213	(0.3593–2.3622)	0.864
Age-Sex strata:			
Male 15–19	1		
Male 20–24	2.8045	(2.1935–3.5858)	<0.001
Male 25–29	3.6241	(2.7234–4.8226)	<0.001
Male 30–34	3.5352	(2.4851–5.0292)	<0.001
Male 35–39	3.0689	(2.0906–4.5048)	<0.001
Male 40-44	2.0991	(1.3477–3.2695)	0.001
Male ≥ 45	2.0741	(1.3905–3.0939)	<0.001
Female 15–19	4.8153	(3.8737–5.9857)	<0.001
Female 20–24	7.4132	(5.9423–9.2482)	<0.001
Female 25-29	6.9468	(5.4606–8.8376)	<0.001
Female 30–34	4.5345	(3.4314–5.9923)	<0.001
Female 35-39	2.9221	(2.1495–3.9723)	<0.001
Female 40-44	2.4351	(1.7985–3.2972)	<0.001
Female ≥ 45	1.6118	(1.1882–2.1866)	0.002
Area of residence:			
Rural	1		
Peri-urban	1.3389	(1.2126–1.4785)	<0.001
Urban	1.1789	(0.9196–1.5113)	0.194
Household wealth quintile:			
Poorest	1		
2nd poorest	1.0144	(0.8903–1.1559)	0.830
3rd poorest	1.0219	(0.8943–1.1677)	0.750
4th poorest	1.0161	(0.8852–1.1663)	0.821
Wealthiest	0.9008	(0.7697–1.0541)	0.193
No. of household changes:			
None	1		
Once	0.8747	(0.7448–1.0273)	0.103
Twice or more	1.2513	(0.9488–1.6502)	0.112
Seroconversions N	2,309		
At-risk Individuals N	15,304		
Exposure Episodes N	163,322		

Hazard ratio (HR), Confidence interval (CI). SE adjusted for household clusters.

Table 5.5: Results of multivariable analysis for the effect of household ART coverage (one or more co-residents) on HIV seroconversion hazard

5.4 Discussion

This study has shown that for each increase of ten percentage points in opposite-sex household antiretroviral therapy coverage, the HIV acquisition hazard was reduced by 6% (95% CI 2–9), after controlling for other factors. This effect size translates into large reductions in HIV acquisition hazards when household antiretroviral therapy coverage is substantially increased–e.g., an increase of 50 percentage points in household antiretroviral therapy coverage (eg, from 20% to 70%) reduced the hazard of HIV acquisition by 26% (95% CI 9–39). Importantly, these results show that the preventive effectiveness of antiretroviral therapy can persist in social contexts in which stable sexual partnerships are difficult to identify, occur late in life, or are not the norm. This study provides the first real-world evidence for the preventive effectiveness of antiretroviral therapy within the household setting (panel).

I did not do a systematic review of the scientific literature, but referred to three previously published systematic reviews (Loutfy et al., 2013; Baggaley et al., 2013; Anglemyer et al., 2013) (synthesizing evidence from a total of one randomized controlled trial and nine observational studies), which showed that antiretroviral therapy substantially reduced or prevented HIV transmission among serodiscordant couples. The authors of two reviews (Cohen et al., 2013; Smith et al., 2012) concluded that ecological studies have methodological limitations, and that the population-level preventive benefit of antiretroviral therapy has yet to be proven. Results of one study (Tanser et al., 2013) showed that high antiretroviral therapy coverage was associated with a reduction in individual risk of HIV acquisition at the community level. I searched PubMed for reports published in English between January 1, 2004, and December 1, 2013, using the search terms 'antiretroviral therapy', 'prevention', and 'household'. I did not identify any studies that assessed the association between risk of HIV acquisition at the individual level and household antiretroviral therapy coverage.

This study had several limitations. Although I used linked clinical and population-based cohort data, I cannot completely rule out the effect of unobserved confounding on these results. A better approach to address confounding would be a randomized control trial, but this strategy would not be possible at the household level for ethical and methodological reasons. However, by controlling for same-sex antiretroviral therapy coverage in the household, I do account for unobserved factors at the household level that affect both opposite-sex and

same-sex coverage and could confound the observed relation between opposite-sex coverage and HIV acquisition. Such factors include the conscientiousness of household members, attitudes towards risk, and attitudes towards health, which are highly plausible confounders in this study, but difficult to measure directly.

This inability to individually link HIV-uninfected individuals to sexual partners outside the household, along with the possible migration of sexual partners outside of the study area, makes accurate measurement of the preventive effectiveness of antiretroviral therapy difficult. Since a subset of HIV-infected individuals (who might or might not be on antiretroviral therapy) in this cohort did not reside in the same household as their uninfected sexual partner and were therefore excluded from the analysis, this finding should be regarded as a minimum estimate of the preventive effectiveness of antiretroviral therapy.

In this study, I included a coresident member in the measure of household antiretroviral therapy coverage if his or her date of antiretroviral therapy initiation was before a residency in a household and if his or her clinic follow-up status was still active during the residency period. I therefore could have further underestimated the preventive benefit of antiretroviral therapy since I did not account for patients failing antiretroviral therapy. This study provides further evidence that treatment with antiretroviral therapy significantly reduces the risk of onward transmission of HIV in a real-world setting in sub-Saharan Africa. Public promotion of the preventive benefits of antiretroviral therapy could help to motivate individuals to learn their HIV status and seek treatment. Adherence to antiretroviral therapy is more likely to be sustained if HIV-infected individuals are aware that the therapy will protect their sexual partners from acquiring the infection. Similarly, the knowledge that antiretroviral therapy can provide protection from HIV acquisition could motivate HIV-uninfected individuals to persuade their infected coresident partners to initiate antiretroviral therapy, improving the long-term use of life-saving drugs within the household.

Important strengths of this study include the use of one of the world's largest HIV incidence cohorts and the ability of this data and study design to capture the changing demographic conditions of an HIV-uninfected individual's living arrangements over time. In this respect, this study is unique because it uses information about HIV serostatus and antiretroviral therapy status among coresident household members to test the treatment-as-prevention hypothesis in a real-world setting in sub-Saharan Africa. Awareness that

antiretroviral therapy can prevent transmission to coresident sexual partners could motivate individuals to disclose their HIV status and to seek and adhere to treatment, improving the long-term use of live-saving antiretroviral therapy.

Chapter 6

Socio-demographic and Structural Predictors of Poor ART Adherence

6.1 Introduction

In this chapter I turn to an examination of the survival benefits of ART, focusing specifically on the topic of treatment adherence. High adherence to ART can dramatically improve the health and mortality outcomes of HIV-infected patients (Nachega et al., 2007; Paterson et al., 2000; Bangsberg et al., 2000), and prevent the onward transmission of HIV (Cohen et al., 2011; Baggaley et al., 2013; Tanser et al., 2013). As a result, efforts to optimize the efficacy of ART in South Africa and elsewhere will be critically dependent on the ability of the public health-care sector to start and then ensure that patients remain adherent to their medications (Nachega et al., 2013). Unfortunately, a significant proportion of patients do not consistently adhere to their medications for reasons discussed in greater detail in Section 6.2. In this chapter I examine the set of socio-demographic and structural variables that are associated with ART adherence in a rural South African community. In addition, I assess whether the predictive information of these variables can be used to augment the clinical detection of imperfect adherence in resource-limited health-care settings.

The data for this analysis comes from the Hlabisa HIV Treatment and Care Programme, which is a decentralized health-care program established by the South African Department of Health (DOH) and the Africa Centre to provide ART free of charge to eligible HIV-infected patients. The start of the HIV program coincides with the nation-wide launch of the DOH's Comprehensive Management and Treatment Plan in 2004 (Houlihan et al., 2011). The scale-up of ART to more than 6 million people through this treatment plan means that a large number of people who are socially and economically marginalized will enter into the

public health-care system. I argue that the ability of patients to maintain their treatment schedules will be continually tested in social conditions characterized by a lack of resources and poverty. In such contexts, patients are unlikely to have adequate financial support to travel to the clinic; or be able to access main routes or motorized transport to easily reach the clinic; or they may have to migrate frequently in search of employment, and therefore miss scheduled clinic visits to obtain their medications. Low levels of health literacy and a lack social support are likely to further compromise adherence; and woman may be more likely to experience the adverse consequences associated with the open use of treatment in the household. These socio-demographic and structural factors are often recognized as the major barriers to treatment adherence in the sub-Saharan African context.

My aim in this chapter is to investigate whether the types of broad, macro-social level factors described above are statistically associated with ART adherence. Further, I suggest that a patient's socio-demographic information, along with the structural factors that may obstruct his or her interaction with the clinic setting, can be used by health-care workers to improve and consolidate treatment-related services. In this regard, I aim to assess if such socio-demographic and structural information can augment a laboratory method—CD4 cell count monitoring—to identify issues related to inconsistent ART usage. I discuss the CD4 count monitoring method in more detail below.

In this analysis, I use viral load count as a biomarker (or proxy) for ART adherence. A viral load is a measure of the number of HIV copies in a cubic centimeter of blood. Viral load count is used to assess the degree of virologic compromise in a patient. Briefly, HIV has a high rate of replication and produces millions of copies of itself every day. ART is designed to keep the rate of HIV replication as low as possible for as long as possible (Stott et al., 2012). High adherence to ART is the most important predictor of virologic suppression, which indicates that the amount of virus within the patient is at a low level (typically <400 copies/ml) (Ford et al., 2010; Rosenblum et al., 2009; Arnsten et al., 2001; Paterson et al., 2000; Bangsberg et al., 2000). Otherwise, persistent viral load counts >1000 copies/ml is a strong indication that a patient has *virologic failure* and is therefore not adhering to—or even taking—their ART medications (Roberts et al., 2012).[1]

[1] For example, patients who have treatment interruptions within the first three months of initiating ART are more likely to have viral load counts >1000 copies/ml six months later (Meresse et al., 2014).

My decision to use viral load as the outcome variable of this analysis is based on a number of scientific studies that have identified high adherence to ART as a primary determinant of virologic suppression (Ford et al., 2010; Wilson et al., 2009; Orrell et al., 2007; Nachega et al., 2007). For this analysis, I define two consecutive viral load counts >1000 copies/ml as an indicator of virologic failure and therefore imperfect or non-adherence to ART (see Section 6.3). This definition of virologic failure is consistent with WHO ART treatment guidelines updated in June 2013 (WHO, 2013). This decision is further supported by the use of viral load measurements to validate self-reported ART adherence (Usitalo et al., 2014; Simoni et al., 2006; Levine et al., 2006; Bangsberg, 2008). Various methods or techniques to measure adherence, most notably self-reporting, electronic pill counting, or pharmacy refill records, tend to be inaccurate or involve complicated logistics. Furthermore, these measures cannot completely determine whether the medications have been physically ingested by the patient (Kagee and Nel, 2012). For these reasons, viral load monitoring is often promoted as the recommended method or gold-standard for assessing treatment adherence (Hamers et al., 2012b; Gupta et al., 2009; Keiser et al., 2011).

There is a close relationship between a patient's viral load and CD4 cell count. A CD4 cell count is a measure of the number of T-lymphocyte cells in a cubic milliliter of blood (cells/µl). HIV destroys CD4 cells, which play an important role in the functioning of the immune system. A CD4 count is therefore used to indicate the degree of immunological compromise in a patient. For example, patients with CD4 counts <50 cells/µl have a 50% annual mortality rate, while individuals with counts <200 cells/µl have mortality rates of 10% to 15% per year (Zijenah and Katzenstein, 2002; Volberding et al., 2012; Gilks et al., 2006; Lawn et al., 2005). CD4 count is further used to determine the risk of opportunistic infections, to assess prognosis, and to decide when the patient is eligible for ART initiation. Importantly, high adherence to ART is closely associated with the health of a patient's immune system, with continuous recovery for up to 7 years after initiation (Sempa et al., 2013). Research has also shown that patients who have a higher a CD4 count at the date of initiation are likely to have a better treatment response at 12 months (Anude et al., 2013; Ramadhani et al., 2007; Djomand et al., 2003; Elul et al., 2013).

Because persistently high viral load results in a decline in CD4 cells, WHO guidelines recommend that CD4 monitoring can be used to identify patients who have virologic failure

(WHO, 2013).[2] However, there is a large debate as to whether CD4 count monitoring should be used for this purpose. A number of studies have shown that CD4 monitoring lacks the sensitivity to accurately detect patients who have virologic failure (Reynolds et al., 2012, 2009; Castelnuovo et al., 2009; Mee et al., 2008; Moore et al., 2008).[3] For this chapter, I include the contested CD4 count predictor in the analysis—hoping to avoid the current debate surrounding this laboratory measure for now—for two reasons. First, I wish to examine the magnitude of the socio-demogaphic and structural variables in comparison to this biological level measure. Second, the socio-demographic and structural variables evaluated in this analysis are not considered to be exclusive or sufficient predictors of virologic failure. My aim in this analysis, rather, is to assess whether information on a patient's socio-demographic characteristics, including his or her interaction with the clinic setting, can be used to augment existing laboratory methods to assess patient response to ART.

I undertake this analysis in two parts. I first use a Cox proportional hazards model to examine the time to virologic failure conditional on the 1) socio-demographic, 2) structural, and 3) CD4 count variables. I specifically use this statistical approach to address potential bias in longitudinal cohort studies that may result from patient loss to follow-up or mortality. Further, I use the complexity and depth of the Africa Centre data to allow for some of the socio-demographic and structural factors—particularly, migration outside of the study area—to vary over time. I specifically undertake the Cox proportional hazards model to assess the inferential association between these predictors and the time to virologic failure.

I then turn to an evaluation of the diagnostic performance of the socio-demographic, structural, and CD4 count variables. I recode all time-varying predictors as constants, which reflect, for example, the number of times migrated outside of the study area, the duration of ART therapy, or the overall number of clinic visits from the date of ART initiation to the date of censorship, etc. CD4 count was estimated as a monthly change for each patient using a fixed effects model. I argue that these recoded variables are likely to

[2] For example, the WHO's *Consolidated guidelines on the use of antiretroviral drugs for treating and Preventing HIV infection* (WHO, 2013) states that there is still insufficient evidence for the survival benefit of viral load monitoring over CD4 or clinical monitoring.

[3] The authors of the cited studies propose that viral load monitoring alone be used to monitor patient response to ART. The debate surrounding these two monitoring strategies is explored in greater detail in Chapter 7 of this dissertation.

be more reflective of the information presented by the patient or database records to the health-care worker during routine clinic visits. I use a logistic regression model to examine the association between the virologic failure outcome and the socio-demographic, structural, and CD4 count variables. I then use a receiver operating characteristics (ROC) analysis to assess the predictive power of the logistic regression submodels, and to classify patients who are at low, medium, or high risk of virologic failure. The ROC method is frequently used in medical and epidemiological research, but may be unfamiliar to the sociological audience. My justification for the use of the logistic regression and ROC analyses is to evaluate if the socio-demographic and structural information of the patient can be used in conjunction with existing laboratory methods (i.e., CD4 count monitoring) to facilitate the detection of virologic failure. Ideally, my approach is one that combines the use of both social and clinical data to facilitate current health-care efforts to achieve this purpose.

6.2 The socio-demographic and structural barriers to ART adherence

There are a number of behavioral, socio-demographic, and structural barriers that are associated with imperfect adherence to ART. Barriers related to the behavioral level may include a patient's fear of disclosure, substance abuse, forgetfulness, suspicion of treatment, treatment complexity, the number of pills required to take daily, food insecurity, and work and family responsibilities (Kagee et al., 2011; Musumari et al., 2014, 2013; Kekwaletswe and Morojele, 2014; Morojele et al., 2013; Lyimo et al., 2014; Nyamhanga et al., 2013; Mills et al., 2006). Researchers have identified a number of socio-demographic or structural level barriers that make adherence to treatment difficult in the sub-Saharan African context. In a systematic review, (Peltzer and Pengpid, 2013) report that having a low income, a lower level of education, and being unemployed are negatively associated with ART adherence. However, there is a lack of definitive or conclusive support for a clear association between socioeconomic status and treatment adherence in low- and middle-income countries where ART is freely available. Braitstein et al. (2006) find that ART is most effective when it is administered for free to patients, although these gains are potentially lost the longer patients are on treatment due to a number of the factors listed above. In South Africa,

treatment retention has decreased over time: as few as 64% of patients initiating ART between 2002 and 2007 were retained in care at 36 months and that this number was lower (50%) for individuals living in rural areas (Cornell et al., 2010).

Socioeconomic status may affect treatment adherence through other factors not specifically related to income, education, or employment status. For example, patients typically have to spend time and money to travel to the health-care clinic to collect their medications, a lifelong process given the nature of HIV and its progression to AIDS. For this reason, indicators related to travel and transport are often considered to be important predictors of ART adherence, along with patient mobility and migration. Research has shown voluntary or forced migration to be an important predictor of adherence in sub-Saharan Africa. One South African study reports that patients often had to travel to family events, and were reluctant to take their medications around distant family members (Coetzee et al., 2011). In a Kenyan study, 68% of patients identified being away from home as the most important factor that affected the timing of ART doses; and 59% of the patients who lived outside of the municipality (where treatment was easily accessible) had poor adherence. In a study from Botswana, 13% of the patients reported having to travel or migrate as a barrier to adherence, and the frequency of required visits to the clinic was also cited as a significant reason for inconsistent treatment use. Approximately 54% of the study participants reported having traveled or lived in more than one place since the start of their treatment, which was identified as disruptive to their treatment schedule (Weiser et al., 2003). In a Ugandan study, 11% of patients reported traveling away from home to significantly impact treatment adherence (Byakika-Tusiime et al., 2005).

Marital status and issues related to gender inequality within the household have been identified with poor ART adherence. In sub-Saharan Africa, the sexual division of power—the product of a patriarchal social system—generally limits the ability of female partners to engage in positive treatment behaviors. This power differential has important implications for the efficacy of ART, particularly because women are unlikely to ensure that their HIV-infected male partners adhere to treatment. For example, fear of partner reprisal may lead women to discontinue or undermine their treatment fidelity. In a qualitative study of 78 participants in Zimbabwe, Skovdal et al. (2011) report that social constructions of

masculinity resulted in husbands interfering with their wives' treatment schedule. HIV-infected women were also unable to fully inform their husbands of their status and to openly comply with their treatment requirements. One Ugandan study found that patients who were single and never married were more likely to adhere to ART (Byakika-Tusiime et al., 2005). In general, research has shown that women who had disclosed their status to their husbands were more likely to accept treatment initiation and return for treatment counseling (Msuya et al., 2008; Farquhar et al., 2004; Msuya et al., 2006; Semrau et al., 2005).

An unlikely source of poor treatment adherence in the study area may come from the provision of disability grants by the South African government at public health-care facilities. Disability grants can be collected by patients who have CD4 count <200 cells/µl for a period of six months. The grants are motivated by the idea that ART will increase CD4 counts and enable the patient to return to work after an improvement in health (Natrass, 2004). Prior research has reported that patients may sometimes deliberately stop taking ART in order to maintain a low CD4 count and therefore re-qualify for the disability grant (Coetzee et al., 2011).

Alongside the socio-demographic predictors are the structural barriers that reflect the difficulties a patient experiences in his or her interaction with the health-care environment. These structural barriers describe either the institutional characteristics of the treatment clinic or the patient's living space that facilitate or disrupt efforts to access and collect medications on a frequent basis. For example, a patient may have to overcome physical obstacles (such as distance and multiple transport routes) to reach the treatment clinic, which may be overly expensive, time consuming, or require the scheduling of time off from the workplace. For this reason, travel to the clinic is often recognized as an important barrier to adherence. Coetzee et al. (2011) report that treatment adherence is influenced by transport difficulties in South Africa that include disruptions to schedules and taxi routes that do not take patients all the way to the clinic. Research by Siedner et al. (2013) found that GPS-measured distances, rather than self-reported distance, to clinic was highly correlated with poor adherence to ART. The frequency of clinic visits, duration between clinic visits, and change of clinic are measures that are likely to reflect a patient's interaction

with the treatment setting, and may be strongly associated with the ability to adhere to ART.

6.3 Methods

6.3.1 Setting and participants

Data was collected from patients presenting at one of 17 primary health-care clinics and the local hospital (Hlabisa) in the study area (Houlihan et al., 2011) between 2004 and 2013. ART was made available free of charge through the HIV Treatment and Care Programme to patients who met treatment eligibility criteria previously outlined in Section 5.2 of this dissertation. Patient demographic and clinical information was collected through a standardized form at routine clinic visits. CD4 count measures were taken every 6 months (Houlihan et al., 2011). Prior to 2010, viral load was measured every six months and repeated after three months if patient viral load was >5000 copies/ml. After 2010, viral load was measured at month 6 and month 12, and then every 12 months if viral load remained <400 copies/ml. Viral load >1000 copies/ml resulted in a repeat measurement every three months (Manasa et al., 2013). Patient data was entered and stored into the Africa Centre's ART Evaluation and Monitoring System (ARTemis).

6.4 Statistical analysis

Imperfect adherence was determined using WHO criteria (WHO, 2013) for virologic failure, defined as a patient's first two successive viral load counts >1000 copies/ml after initiating ART (thus indicating persistent viremia). I use the virologic failure outcome as a biomarker (or proxy) for adherence to ART, and justify this decision in Section 6.1. Patients had to be on ART for a minimum of 6 months,[4] and all viral load measures were selected 30 days after the ART initiation date (to allow for viral load response to treatment) until the date of virologic failure or last clinic visit.

[4] This time frame is recommended by WHO criteria (WHO, 2013).

6.4.1 Cox proportional hazards analysis

I use a Cox proportional hazards model to evaluate the time to virologic failure and to address potential biases related to patient drop-out or mortality while under observation. Importantly, I use this model to quantify the inferential association between the time to virologic failure and the independent variables of the socio-demographic, structural and CD4 count submodels. The socio-demographic submodel includes age, sex, employment, highest education level, and history of migration out of the study area. The structural submodel includes the distance to clinic or main road, previous use of ART, frequency of clinic visits, duration between clinic visits, and change of clinic since the date of initiation. I specified age, migration, distance to clinic and main road, and duration between clinic visits as time-varying predictors. Distance to clinic or main road was considered time-varying to account for changes in household residency. As discussed in Chapter 5, a strength of Cox proportional hazards model is its ability to account for changes in patient mobility and migration within and outside of the study area. For the third submodel, I assess the association between CD4 cell count, a time-varying predictor, and time to virologic failure (and justify this inclusion in Section 6.1 of this chapter).

6.4.2 Logistic regression analysis

I move from the inferential analyses of the Cox proportional hazards analyses to evaluate the predictive performance of the socio-demographic, structural, and CD4 count submodels. To do this I recoded the time-varying predictors used in the socio-demographic and structural submodels as constants for the logistic regression analyses. For example, I coded migration as the number of times a patient migrated out of the study area, and employment was calculated as the proportion of time employed while under observation. I used an individual fixed effects model to capture the change in CD4 cell count as a single estimate for each patient using methods discussed in the Appendix (page 181). This estimate reflects the monthly change in a patient's CD4 count, expressed as a slope or coefficient.

The logistic regression model is briefly outlined below. Let Y_j be a single, unobserved response for the jth patient ($j = 1, \ldots, n$), where

$$Y_j = \begin{cases} 1 & \text{the patient has virologic failure} \\ 0 & \text{the patient does not have virologic failure.} \end{cases}$$

Let $\pi(x) = Pr(Y = 1|X = x)$ be the conditional probability that a patient has virologic failure, given the covariate value $X = x$. We consider the response Y to be a single random variable with a Bernoulli distribution. Let $y_1, \ldots, y_n$ be the realizations of the $Y_1, \ldots, Y_n$ independent Bernoulli random variables. Then

$$(Y_j|X = x_j) \sim \text{Bin}(1, \pi(x_j)) \tag{6.1}$$

has a binomial distribution, and $\pi(x_j)$ is the probability that the jth patient will have virologic failure for a fixed value x_j (Weisberg, 2005). An important assumption of this binomial distribution is that i) each patient has the same marginal probability π of having virologic failure and ii) the outcomes for all patients are independent. We can express the logit of $\pi(x_j)$ for the univariate model as:

$$\log_e \frac{\pi(x_j)}{1 - \pi(x_j)} = \beta_0 + \beta_1 X_j. \tag{6.2}$$

which produces $\boldsymbol{\beta}$ coefficients in the log-odds form and where $\beta_1 = 0$ indicates that the response variable Y is independent of the predictor variable X. It is easier to interpret the $\boldsymbol{\beta}$ coefficients as the odds that a patient will have virologic failure. To do this we exponentiate both sides of (6.2) and get:

$$\frac{\pi(x_j)}{1 - \pi(x_j)} = \exp(\beta_0 + \beta_1 X_j). \tag{6.3}$$

Equation (6.3) is a multiplicative model where the odds is in the range $[0, \infty)$, and where $e^{\beta_1} = 1$ indicates that the response variable Y is independent of the predictor variable X. Thus, a one unit change in CD4 count slope changes the odds of a patient having virologic failure by a factor of e^{β_1}. The predicted probability (pp) that a patient will have virologic failure for a fixed value x_{kj} is:

$$\pi(x_j) = \frac{\exp(\beta_0 + \beta_1 X_{1j} +, \ldots, +\beta_k X_{kj})}{1 + \exp(\beta_0 + \beta_1 X_{1j} +, \ldots, +\beta_k X_{kj})}, \tag{6.4}$$

which maps the linear predictor $Y = \beta_0 + \beta_1 X_{1j} +, \ldots, + \beta_k X_{kj}$ onto the [0,1] interval for the multivariate model (for k number of independent variables) (Fox, 2008). As discussed, the predicted probabilities give the probability of virologic failure for each patient conditional on the independent variables of the submodel. We can assess the predictive performance of the submodel by performing an AUC analysis, which I describe in greater detail in the next section.

6.4.3 ROC analysis

I use a receiver operating characteristics (ROC) analysis to assess the predictive performance of the socio-demographic, structural, and CD4 count logistic regression submodels. An ROC analysis goes beyond the interpretation of odds and hazard ratios, and their p-values, to determine the error rate of a given classification schema. The application of the ROC analysis in this chapter can be demonstrated with the following example. Having performed a logistic regression using the independent variables for the socio-demographic submodel, I decide to classify all patients with a predicted probability of virologic failure less than a 0.40 cut-point as belonging to a low risk group and all patients with a predicted probability greater or equal than a 0.40 cut-point as belonging to a high risk group. To what extent does this classification schema correctly identify the proportion of patients in the sample that truly have virologic failure? Since no predictive model is perfect, it is likely that this classification schema will have some degree of error: not all patients in the high risk group will have virologic failure; and some patients in the low risk group will have virologic failure.

ROC analyses are often used by the medical decision-making community to evaluate the performance of diagnostic systems (Swets et al., 2000). It is a method for selecting classifiers based on their performance (Fawcett, 2006; Brown and Davis, 2006). Figure 6.1 shows an example of a classification model, called a contingency table or confusion matrix, using only two classes. In this example, the two classes produce four possible outcomes by mapping observed or known instances (the true class) to the predicted (hypothesized) class. If an instance is positive (+) and has been classified under the hypothesized class as positive (+), then it is a true positive. If an instance is positive (+) but has been classified under the hypothesized class as negative (−) then it is a false negative, etc.

		Hypothesized Class	
		−	+
True Class	−	True Negative	False Positive
	+	False Negative	True Positive

Figure 6.1: Example of a confusion matrix showing four possible outcomes

Consider the confusion matrix in Table 6.1, which shows toy data for the example presented at the beginning of this section. The true class consists of the patients who have or do not have virologic failure using the definition for first two consecutive viral load measures >1000 copies/ml. These patient outcomes have been observed in the data. The hypothesized class are the patients that are classified under a high or low risk group based on their predicted probabilities (obtained from the logistic regression analysis).

	Group		
Failure	Low Risk	High Risk	Total
No	4,104	209	4,313
Yes	944	317	1,261
Total	5,048	526	5,574

Table 6.1: Example of a confusion matrix showing the outcomes classified by virologic failure and risk group status

Using this classification schema, each patient is mapped to one of four possible and distinct outcomes, which correspond with Figure 6.1. These are:

- True negatives: all patients in the low risk group are correctly classified as not having virologic failure ($n = 4104$).
- True positives: all patients in the high risk group are correctly classified as having virologic failure ($n = 317$).
- False negatives: patients in the low risk group have been incorrectly classified as not having virologic failure ($n = 944$).
- False positives: patients in the high risk group have been incorrectly classified as having virologic failure ($n = 209$).

The cells in Table 6.1 can be used to determine the error rate of the low/high risk group classification schema. The sensitivity is a measure of how well the classification schema (using the low/high risk group categories) identifies true positives, that is, the patients that were observed in the sample to have virologic failure. Sensitivity, is defined as the number of true positives in a group over the total number of positives. Looking at Table 6.1, the sensitivity for the high risk group is:

$$\frac{\text{positives correctly identified}}{\text{total positives}} = \frac{317}{1261} \times 100 = 25.14\%. \tag{6.5}$$

If we used membership of the high risk group to 'diagnose' virologic failure, then we would only correctly identify 25% of the sample as truly having virologic failure, which is a poor sensitivity. From this example, the selection of the 0.40 cut-point to define a low or high risk group does not appear to adequately identify patients who truly have virologic failure.

The specificity is a measure of how well the classification schema identifies true negatives, that is, the patients in the sample that were observed to not have virologic failure. The specificity for the classification schema using membership of the high risk group is determined first by the false positive (fp) rate, which is the number of negatives incorrectly classified in the high risk group over the total number of negatives:

$$\frac{\text{negatives incorrectly classified}}{\text{total negatives}} = \frac{209}{4313} = 0.048 \tag{6.6}$$

From this the specificity is computed as $1-(\text{fp rate}) = (1-0.048)\times 100 = 95.2\%$. Thus, the high risk group threshold can detect 95.2% of the patients that truly do not have virologic failure. The classification rate measures all the cases correctly classified, which is:

$$\frac{\text{true positives + true negatives}}{\text{total cases}} = \frac{4104+317}{5574} \times 100 = 79.31\%.$$

Table 6.2 shows the sensitivity, specificity, and classification rates for the low and high risk groups. Technically, each group is called a threshold candidate because the sensitivity and specificity measures are computer for all instances $\geq$ or $>$ than a selected cut-point. Table 6.2 is important because it can be used to graph each of the threshold cut-points, as shown in Figure 6.2. The point in the top right corner represents a sensitivity=100% and a specificity=0%, which is the $\geq$ `Low risk` group threshold (as labeled). Thus, all low and high risk groups would be diagnosed as having virologic failure, thereby identifying

all true positives, but failing to identify any true negatives. The point in the bottom left corner represents a sensitivity=0% and a specificity=100%, indicating the $>$ `High risk` group threshold. The remaining point represents the threshold for the $\geq$ `High risk` group threshold, which was computed in (6.5) and (6.6) above. The area under the points, called the AUC, is computed using the trapezoidal rule, and gives an objective measure of the predictive performance of the classification schema. This area can be maximized by selecting the appropriate thresholds that give the highest AUC. A strong predictive performance is set at 0.80 or greater (thus an AUC of 0.60 confirms the weak predictive power of the current risk group classification used in the example).

Candidate Threshold	Sensitivity	Specificity	Correctly Classified
$\geq$ Low	100.00%	0.00%	22.62%
$\geq$ High	25.14%	95.20%	79.31%
$>$ High	0.00%	100.00%	77.38%

Table 6.2: Specificity, sensitivity, and classification rate for threshold candidates

6.4.4 Determining the risk group classification schema

In the cited example, I arbitrarily selected a cut-point threshold of 0.40, but how can the criteria for classifying patients under a particular risk group status (or any other classification schema) be more systematically determined? We can use the power of statistical and predictive modeling to define or construct such cut-points. In this chapter, the criteria for determining membership of a risk group (the hypothesized class) are obtained in three steps: 1) Using a logistic regression analysis, regress the virologic outcome on the relevant submodel variables, 2) undertake a post-estimation analysis and obtain a predicted probability of virologic failure (conditional on the submodel variables) for each patient, 3) classify the predicted probability (pp) for each patient under the relevant low, medium, or high risk

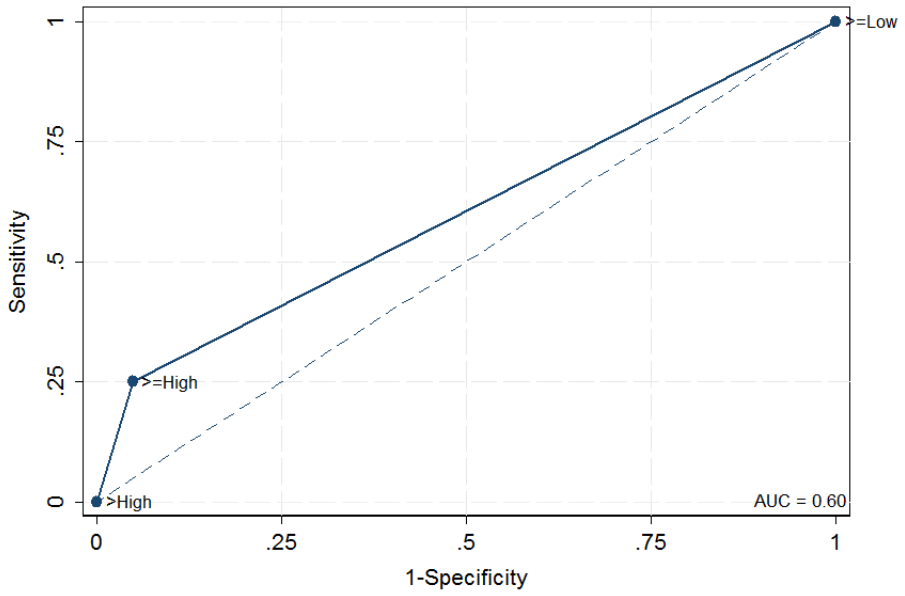

Figure 6.2: Area under the curve (AUC) showing the performance of the classification schema presented in Table 6.2

group. Patients in step 3) are assigned to a risk group using the following algorithm:

$$\text{risk group} = \begin{cases} \text{low if } 0 \geq pp < x \\ \text{medium if } x \geq pp < y \\ \text{high if } y \geq pp \leq 1, \end{cases} \tag{6.7}$$

where $0 < x < y < 1$. The cut-points x and y are selected that give the maximum AUC of an ROC graph.[5] The error rate of the classification schema, which uses the (x, y) pair to determine the low, medium, and high risk groups, is then evaluated using the ROC analysis.

[5] Using the statistical software package Stata (version 12.1), I iterate over incremental values between 0 and 1 for both x and y, and select the pair (x, y) which gives the maximum AUC. An example of the Stata code is given on page 188 of the Appendix.

6.5 Results

There were 6,137 patients in the ARTemis database that initiated ART. Patients on ART for less than 6 months were dropped from the analysis ($n = 2,190$). A further 196 and 226 patients were dropped because they had less than two viral load or CD4 measurements. There were 3,525 patients in the final analytic dataset, of which 2,614 (74.2%) patients were female. The median age was 35 years. There were 510 patients that met the criteria for virological failure, and thus identified as having poor or imperfect ART adherence. On average, patients were exposed to ART for a duration of 35.1 months (i.e., from 30 days after treatment initiation to the virologic failure event or the last clinic visit). The summary statistics for the socio-demographic, structural variables, and CD4 count variables are shown in Table 6.3.

6.5.1 Univariate hazards model

Table 6.4 shows the univariate associations for the Cox proportional hazards model. The hazard ratios for age, education (high school and tertiary education), migration out of the study area, duration on ART, change of clinic and number of clinic visits since initiation, and change in CD4 count were significant at the 0.05 level. Younger patients and patients that migrated outside of the study area were more likely to have an increased hazard of virologic failure. Straight line distance to nearest clinic or main road was not significant at the 0.05 level, although it is unclear if this measure accurately captures the real-time distance (and cost) needed to travel to this destination. For the structural predictors, results show that patients attending more clinic visits after treatment initiation were less likely to have virological failure. A patient was more likely to have virological failure if he or she changed clinics one or more times since initiating treatment. Sample sizes differed for each univariate analysis. I explore these variables in greater detail in the submodel analyses below.

Female	No.	%
No	911	26
Yes	2,614	74
Age category	No.	%
16-	53	2
20-	273	8
25-	665	19
30-	719	20
35-	625	18
40-	1,190	34
Married	No.	%
No	152	80
Yes	38	20
Living with Partner	No.	%
No	157	85
Yes	27	15
Highest Education	No.	%
No School	233	7
Primary School	723	21
High School	1,754	50
Tertiary	815	23
Employed >50% of time	No.	%
No	2,421	69
Yes	1,104	31
Km (line) to level 1 road	No.	%
0-	1,114	32
1-	530	15
2-	207	6
3-	272	8
5-	528	15
10-	874	25

Km (line) to nearest clinic	No.	%
0-	540	15
1-	977	28
2-	729	21
3-	869	25
5-	410	12
Residential migration once or more	No.	%
No	2,255	64
Yes	1,270	36
Out migration once or more	No.	%
No	2,925	83
Yes	600	17
Disability grant	No.	%
No	3,514	100
Yes	11	0
Previous ART	No.	%
Don't know	403	11
No	2,905	82
Yes	217	6
Clinic visit count	No.	%
0-	502	14
2-	795	23
3-	1,098	31
5-	765	22
8-	365	10
Changed clinic	No.	%
No	2,889	82
Yes	636	18

Table 6.3: Summary statistics of socio-demographic, structural and CD4 count variables

	Univariate Model		
	HR	**(CI)**	**p-value**
Male	1.170	(0.962–1.424)	0.116
Age	0.966	(0.956–0.976)	0.000
Highest education: No school	(Ref.)		
Primary school	1.173	(0.720–1.910)	0.522
High school	1.844	(1.171–2.902)	0.008
Tertiary education	1.654	(1.030–2.656)	0.038
Employed	0.862	(0.713–1.042)	0.125
Married	1.514	(0.603–3.800)	0.377
Km to nearest main road	0.987	(0.973–1.001)	0.071
Km to nearest clinic	0.991	(0.943–1.041)	0.713
Migrated out of surveillance area	4.885	(3.196–7.469)	0.000
Migrated out of current residence	2.575	(1.839–3.604)	0.000
Disability grant	1.470	(0.367–5.897)	0.586
Previous ART: No	(Ref.)		
Don't know	0.701	(0.532–0.923)	0.012
Yes	0.880	(0.632–1.225)	0.448
Duration between clinic visits (mths)	1.002	(0.981–1.024)	0.827
Duration of ART (mths)	0.803	(0.791–0.816)	0.000
Changed clinic	1.343	(1.106–1.631)	0.003
Clinic visit count	0.234	(0.212–0.259)	0.000
CD4 Count[a]	0.972	(0.965–0.980)	0.000

[a] For a 20 cell count increase in CD4

Table 6.4: Univariate results for the socio-demographic, structural, and CD4 count predictors of virological failure

6.5.2 Submodel 1: Socio-demographic predictors

For submodel 1 I examine the association between the time to virologic failure and the socio-demographic predictors sex, age, highest level of education, employment, and disability grant received. The Cox proportional hazard results are shown in Table 6.5. Results show that older patients are less likely to have virologic failure when compared with patients aged 16–19 years, holding all else constant. Migration out of the study area is associated with a 4.03 (95% CI: 2.66–6.10) increase in the hazard of virologic failure, holding all else constant. Patients with a history of employment were less likely to have virologic failure.

	Submodel 1		
	HR	**(CI)**	**p-value**
Male	1.383	(1.131–1.689)	0.002
Age:			
16–19	(Ref.)		
20–24	0.351	(0.200–0.616)	0.000
25–29	0.387	(0.235–0.638)	0.000
30–34	0.338	(0.205–0.557)	0.000
35–39	0.312	(0.187–0.521)	0.000
$\geq$ 40	0.171	(0.102–0.286)	0.000
Highest education:			
No school	(Ref.)		
Primary school	1.038	(0.636–1.695)	0.882
High school	1.216	(0.757–1.954)	0.419
Tertiary education	1.163	(0.710–1.907)	0.548
Employed	0.820	(0.675–0.996)	0.045
External migration	4.025	(2.658–6.096)	0.000
Disability grant received	1.905	(0.474–7.667)	0.364
Virologic Failure	510		
Total	3,525		
Exposure Episodes	25,459		

Table 6.5: Submodel 1: Cox proportional hazards model output for the socio-demographic variables

Table 8.2 of the Appendix shows the results for the logistic regression model. The AUC (0.57) for the ROC graph was maximized using the cut-points $x = 0.10$ and $y = 0.15$, from which the low, medium, and high risk group categories were constructed. I present the confusion matrix for submodel in Table 6.6, which shows the number and percentage of patients that were classified under each risk group. Table 6.7 shows the sensitivity and specificity for this classification schema. We would identify 90.98% of the patients who truly have virologic failure using the $\geq$ medium risk group threshold (i.e., all medium and high risk patients). This is a strong sensitivity for the $\geq$ medium risk group threshold; however, the very low specificity of 17.51% indicates that only a small number of patients would have been correctly identified as not having virologic failure at this threshold.[6]

[6] As a result, a substantial number of patients would be classified as false positives, and would likely be referred to additional health-care services or monitoring, that would place an unnecessary cost on already

Failure	Risk group							
	Low Risk		Med Risk		High Risk		Total	
	No.	%	No.	%	No.	%	No.	%
No	528	92	1,162	86	1,325	83	3,015	86
Yes	46	8	184	14	280	17	510	14
Total	574	100	1,346	100	1,605	100	3,525	100

Table 6.6: Confusion matrix for submodel 1

Threshold	Sensitivity %	Specificity %	Correctly Classified %
$\geq$ Low Risk	100.00	0.00	14.47
$\geq$ Medium	90.98	17.51	28.14
$\geq$ High	54.90	56.05	55.89
$>$ High	0.00	100.00	85.53

AUC = 0.57

Table 6.7: Specificity and sensitivity for submodel 1

We would only identify 54.90% of the patients that truly have virologic failure under the $\geq$ high risk group threshold (i.e., only patients in the high risk group). Further, the high risk threshold gives a low specificity of 56.05%. The AUC for this submodel is low at 0.57 (see Figure 8.1 in the Appendix), which indicates that the socio-demographic predictors perform poorly in correctly classifying the virologic failure outcomes of patients using the data. This result already confirms the weak effects for the odds ratios shown in Table 8.2. Figure 8.1 in the Appendix plots the sensitivity and specificity for each threshold and shows the area under the curve for the ROC analysis. Figure 6.3 shows the Kaplan-Meier survival curves for each risk group profile.

6.5.3 Submodel 2: Structural predictors

For this submodel I examine the structural predictors associated with virologic failure. I include the distance from the patient's home to the nearest clinic or main road, along with

limited logistic, financial, and human resources in the study area. This issue is explored in greater detail in Chapter 7.

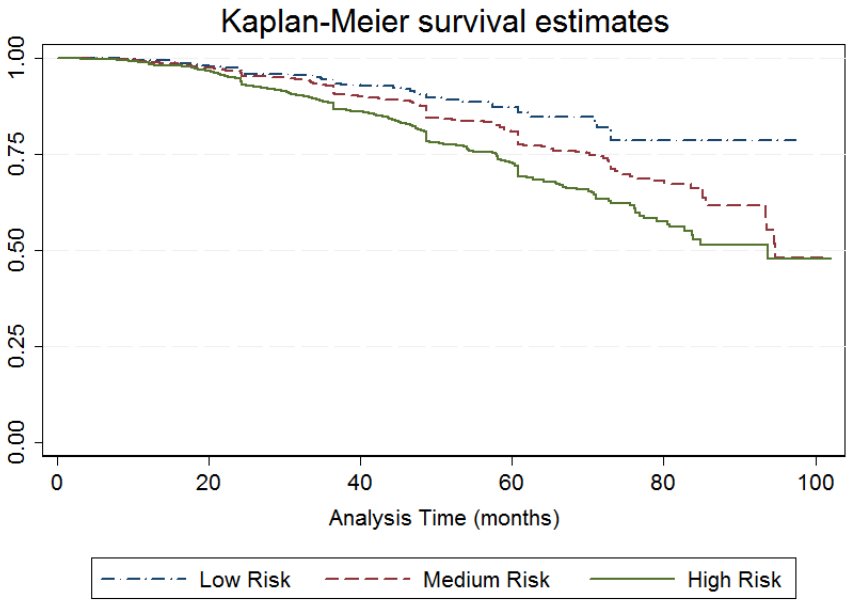

Figure 6.3: Submodel 1: Kaplan-Meier survival estimates for each risk group

other measures related to the patient's interaction with the health-care environment, which include the previous use of ART, duration of time between clinic visits, number of clinic visits, and change in clinic since treatment initiation. Table 6.8 shows the Cox proportional hazard results. Straight line distance to the clinic (or main road, result not shown), previous use of ART, and changed clinic since treatment initiation are not significantly associated with the hazard of virologic failure at the 0.05 level. However, more frequent clinic visits, and shorter time between clinic visits are associated with a reduced hazard of virologic failure. These two variables may indicate a patient's level of interaction with the clinic setting.

I use the predicted probability thresholds of $x = 0.10$ and $y = 0.25$ to determine the risk group categories, as obtained from the maximized AUC of the ROC graph. Table 6.9 shows the confusion matrix, and Table 6.10 shows the sensitivity and specificity of the structural predictors by risk group. We would correctly identify 83.33% of patients that have virologic failure using the $\geq$ medium threshold, with a specificity of 52.54%. The structural predictors perform better than the socio-demographic predictors in correctly classifying patients who

	Submodel 2		
	HR	**(CI)**	**p-value**
Km (line) to nearest clinic	1.030	(0.980–1.082)	0.250
Previous ART:			
No	(Ref.)		
Don't know	0.752	(0.568–0.996)	0.047
Yes	0.886	(0.635–1.237)	0.478
Ave. months between clinic visit	0.891	(0.873–0.908)	0.000
Clinic visit count	0.380	(0.353–0.409)	0.000
Changed clinic	1.169	(0.959–1.424)	0.122
Virologic Failure	510		
Total	3,525		
Exposure Episodes	25,459		

Table 6.8: Submodel 2: Cox proportional hazards model output for the structural factors

	Risk group							
Failure	Low Risk		Med Risk		High Risk		Total	
	No.	%	No.	%	No.	%	No.	%
No	1,584	95	1,247	88	184	42	3,015	86
Yes	85	5	170	12	255	58	510	14
Total	1,669	100	1,417	100	439	100	3,525	100

Table 6.9: Confusion matrix for submodel 2

have virologic failure as reflected by the AUC of 0.77 for submodel 2 (higher than the AUC of 0.57 for submodel 1). Figure 8.2 in the Appendix plots the sensitivity and specificity for each threshold and shows the area under the curve for the ROC analysis. Figure 6.4 shows the Kaplan-Meier survival curves for each risk group profile.

6.5.4 Submodel 3: CD4 count predictor

To more clearly assess the predictive performance of the socio-demographic and structural variables, I examine the association between virologic failure and change in patient CD4 count since treatment initiation. I use an individual fixed effects model to obtain the patient-specific slopes, which represent the monthly change in CD4 cell count and show this distribution in Figure 8.3 of the Appendix: the mean is 8.35 (sd = 16.13) cells/µl per

Threshold	Sensitivity %	Specificity %	Correctly Classified %
$\geq$ Low Risk	100.00	0.00	14.47
$\geq$ Medium	83.33	52.54	56.99
$\geq$ High	50.00	93.90	87.55
$>$ High	0.00	100.00	85.53

AUC = 0.77

Table 6.10: Specificity and sensitivity for submodel 2

month. Table 6.11 shows the results: a 20 cell count increase in CD4 count decreases the hazard of virologic failure by a factor of 0.05 (95% CI: 0.94–0.96), holding all else constant. The hazard of virologic failure is negatively associated with age.

		Submodel 3	
	HR	**(CI)**	**p-value**
CD4 Count[a]	0.951	(0.940–0.962)	0.000
Age:			
16–19	(Ref.)		
20–24	0.445	(0.254–0.781)	0.005
25–29	0.498	(0.303–0.817)	0.006
30–34	0.463	(0.282–0.758)	0.002
35–39	0.400	(0.242–0.662)	0.000
$\geq$ 40	0.205	(0.124–0.340)	0.000
Male	1.102	(0.902–1.345)	0.342
Virologic Failure	510		
Total	3,525		
Exposure Episodes	12,230		

[a]For a 20 cell count increase in CD4

Table 6.11: Submodel 3: Cox proportional hazard model output for the CD4 count, age, and sex predictors

I then ran a logistic regression analysis using the patient-specific changes in CD4 count slope. To make the association between virological failure and the CD4 count slopes more interpretable, I grouped the slopes into categories of <-10; 10 to -1; 0 to 5; and > 5. The CD4 slope categories are shown in Table 8.3 in the Appendix. I then regressed the

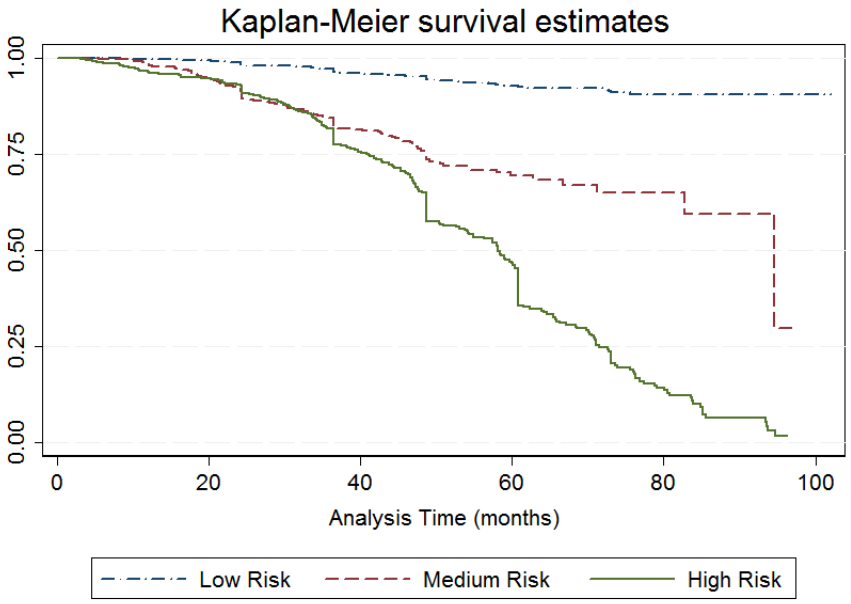

Figure 6.4: Submodel 2: Kaplan-Meier survival estimates for each risk group

virological failure variable on the categorical variable and show the regression output in Table 8.4 of the Appendix. Results show a strong inverse association between CD4 count slope and the odds of virological failure.

I used the predicted probability cut-points $x = 0.10$ and $y = 0.23$ to determine the risk group categories, as obtained from the maximized AUC of the ROC graph for this submodel. Table 6.12 shows the confusion matrix and Table 6.13 shows the sensitivity and specificity for each risk group. We would correctly identify 72.35% of the patients that have virologic failure using the $\geq$ medium risk group threshold, with a specificity of 71.55%. Figure 8.4 in the Appendix plots the sensitivity and specificity for each threshold and shows the area under the curve for the ROC analysis. Figure 6.7 shows the Kaplan-Meier survival curves for each risk group profile.

Failure	Risk group: Low Risk No.	Low Risk %	Med Risk No.	Med Risk %	High Risk No.	High Risk %	Total No.	Total %
No	2,157	94	613	87	245	47	3,015	86
Yes	141	6	93	13	276	53	510	14
Total	2,298	100	706	100	521	100	3,525	100

Table 6.12: Confusion matrix for submodel 3

Threshold	Sensitivity %	Specificity %	Correctly Classified %
$\geq$ Low Risk	100.00	0.00	14.47
$\geq$ Medium	72.35	71.54	71.66
$\geq$ High	54.12	91.87	86.41
$>$ High	0.00	100.00	85.53

AUC = 0.77

Table 6.13: Specificity and sensitivity for submodel 3

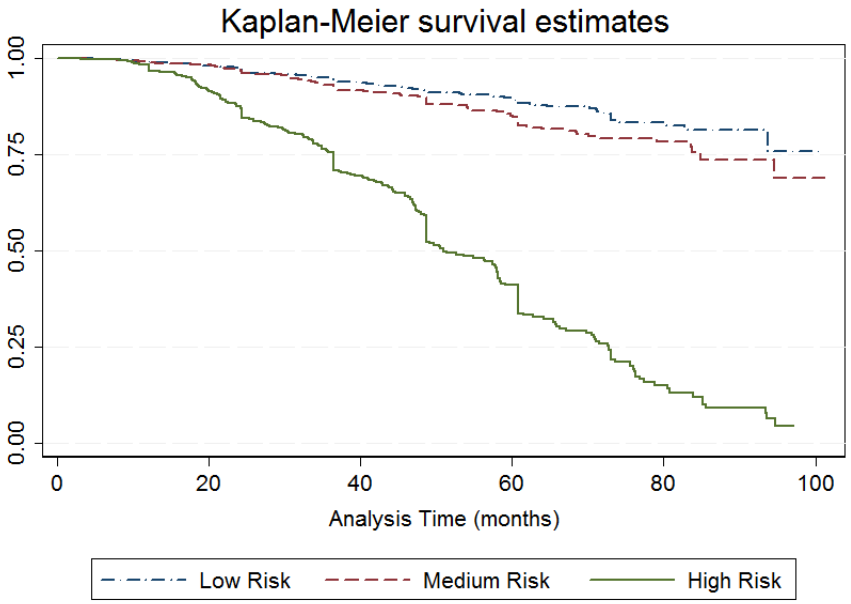

Figure 6.5: Submodel 3: Kaplan-Meier survival estimates for each risk group

Submodel 4: Model selection

I continue to use the maximum AUC of an ROC analysis to select the final submodel for this analysis. To do this I compared the AUC for various submodels. For example, for the first submodel I include only CD4 slope (which gives an AUC of 0.759), in the second model I include CD4 slope and age (which gives an AUC of 0.776), in the third model I select CD4 slope, age, and sex (which gives an AUC of 0.774), and so on. The highest AUC obtained is 0.856 for the following variables: CD4 slope, age, male, proportion of time employed, migrated outside of study area, changed clinic since treatment initiation, number of clinic visits, duration on treatment, and the average time between clinic visits.

	Risk group							
Failure	Low Risk		Med Risk		High Risk		Total	
	No.	%	No.	%	No.	%	No.	%
No	2,197	97	648	84	170	35	3,015	86
Yes	70	3	122	16	318	65	510	14
Total	2,267	100	770	100	488	100	3,525	100

Table 6.14: Confusion matrix for submodel 4

Threshold	Sensitivity %	Specificity %	Correctly Classified %
$\geq$ Low Risk	100.00	0.00	14.47
$\geq$ Medium	86.27	72.87	74.81
$\geq$ High	62.35	94.36	89.73
$>$ High	0.00	100.00	85.53

AUC = 0.86

Table 6.15: Specificity and sensitivity for submodel 4

The logistic regression results are shown in Table 8.5 in the Appendix. The low, medium, and risk groups were determined using the $x = 0.10$ and $y = 0.30$ cut-points that maximized the AUC for the model selection procedure. Table 6.14 and Table 6.15 show the confusion matrix and sensitivity/sensitivity analysis respectively for submodel 4. Figure 6.6 shows

the area under the curve for the ROC analysis and Figure 6.7 shows the Kaplan-Meier survival curves for each risk group profile.

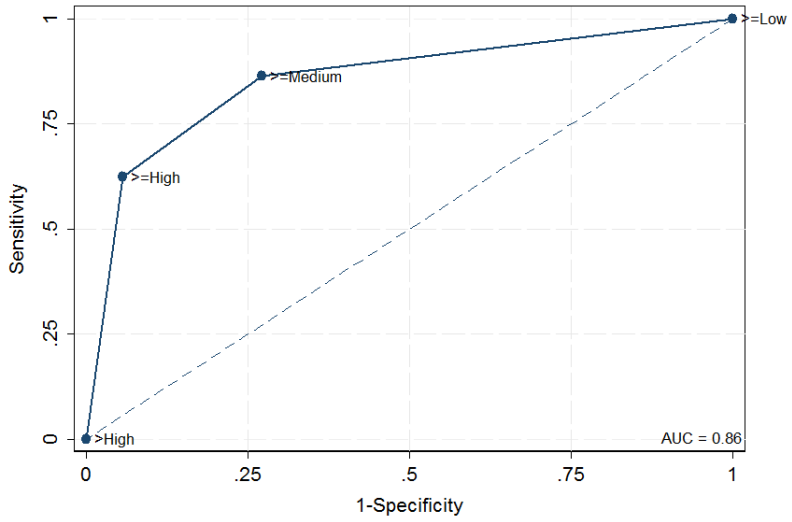

Figure 6.6: ROC graph for submodel 4 (selected predictors)

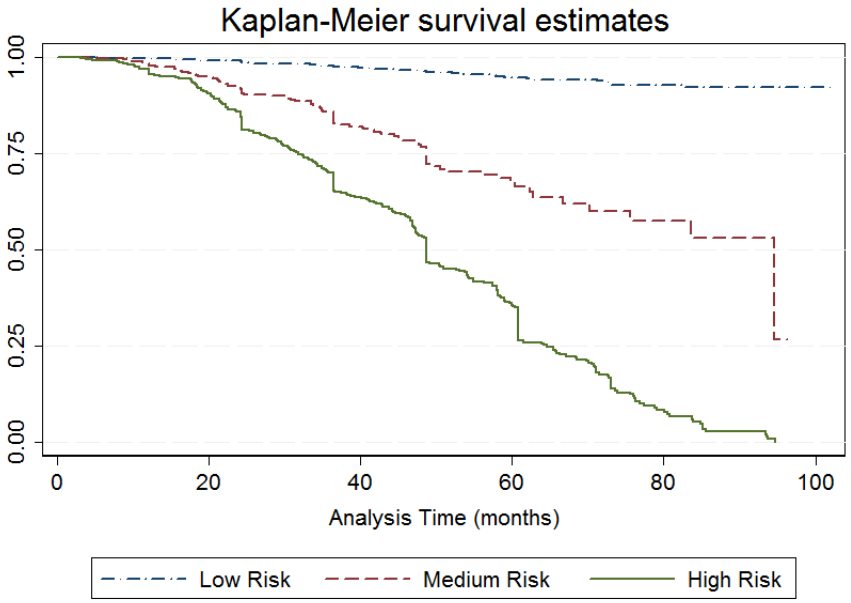

Figure 6.7: Submodel 4: Kaplan-Meier survival estimates for each risk group

6.6 Discussion

In this chapter I have presented an analysis of the socio-demographic, structural, and clinical predictors of virologic failure, which I use as a proxy for ART adherence. Adherence to ART is the single most important determinant of reduced mortality and improved health outcomes in HIV-infected patients, and is critical to preventing the onward transmission of HIV. Imperfect adherence to ART is a significant problem in sub-Saharan Africa because patients typically have to overcome a range of social and structural obstacles in order to take their medications consistently and on a daily basis. I have argued that efforts to optimize the efficacy of ART in South Africa and elsewhere will be critically dependent on the ability of the public health sector to initiate and then ensure that patients remain adherent to their HIV medications. The work presented in this chapter is therefore strongly motivated by the need to understand the socio-demographic and structural predictors that are likely to disrupt or attenuate high adherence to ART. It is hoped that this work can be used to contribute to health-care efforts designed to detect imperfect adherence in resource-limited settings.

I argued in the introduction of this chapter that viral load monitoring offers an accurate method for determining imperfect adherence to ART. We would expect to see viral loads below 400 copies/ml for patients that take their medications on a consistent basis. The use of viral load counts as a biomarker for ART adherence avoids the problems associated with the measure of adherence more generally, which cannot establish for certain whether patients have actually ingested their medications. Viral loads consistently >1000 copies/ml indicate that a patient is not adhering to his or her treatment requirements. For this reason, virologic failure—the presence of two or more viral loads >1000 copies/ml after treatment initiation—was selected as the outcome of this analysis, and as a proxy for imperfect adherence to ART.

I began the analysis by using a Cox proportional hazards model to estimate the hazard of virologic failure conditional on the structural and socio-demographic predictors. The structural predictors measured the degree of interaction between the patient and the treatment and care setting. Multivariate results show that migration out of the study area was most significantly associated with a higher hazard of virologic failure, which confirms the

findings of previous research. Generally, travel or migration away from home results in disruptions to the patient's treatment schedule and the timing of doses (Coetzee et al., 2011; Weiser et al., 2003). The results also show that employed individuals were less likely to have virologic failure, but the remaining socio-demographic variables (except for age) were not statistically significant at the 0.05 level. Previous research has shown that ART adherence in low- and middle-income countries is associated with a higher income, a higher level of education, and being employed. But these predictors are less likely to be salient in contexts where ART is freely available (as is the case in the study area), and the results from the multivariate Cox proportional model appear to confirm this finding.

Results further show statistically significant associations between virologic failure and a patient's interaction with the treatment and care setting. More frequent clinic visits was associated with a reduced hazard of virologic failure. And shorter average time between clinic visits was associated with a decreased hazard of virologic failure. These two results suggest that frequent interaction with the clinic setting is likely to be associated with a reduced hazard of virologic failure. Thus public health-care efforts to ensure routine visits with the health-care setting may help to improve patient response to ART. The logistic regression results also show that increased duration on ART was associated with a greater hazard of virologic failure. This finding confirms what is currently established in the literature—that patients more likely to have poor adherence the longer they are on treatment (Elul et al., 2013; Cornell et al., 2010).

I turned to a logistic regression analysis of the socio-demographic and structural predictors. I ran submodels separately on the socio-demographic and structural predictors, and added an additional model that included age, sex, and change in CD4 count since treatment initiation. My intention was to compare the effect sizes of the socio-demographic and structural variables with a more proximate predictor (i.e., CD4 count), and then ultimately develop a submodel which included the strongest predictors of virologic failure. Results for the socio-demographic submodel show that age was the only significant predictor at the 0.05 level. Migration out of the study area, which had a relatively large effect size in the Cox proportional hazards model, was attenuated but still significant at the 0.05 level. This result should be interpreted with caution, since the logistic regression model did not consider the longitudinal impact of migration on virologic failure. In the case of the Cox

proportional hazards model, I was able to incorporate the duration of migration directly into the estimate of virologic failure through the use of the exposure episodes concept discussed in greater detail in Chapter 5.

Results for the structural predictors submodel show that distance from clinic was not significantly associated with virologic failure. Previous research has shown distance to clinic to be an important predictor of poor adherence (Siedner et al., 2013). In this analysis, distance to the clinic was measured as a straight line from the patient's residence to the clinic. This measure may not accurately capture the cost and time to reach this destination: actual distance by road to the clinic may be longer than a straight line, the patient's residence may not be close to a transport hub, and multiple taxi rides may be required to reach the clinic. The direction of the effects for duration on ART, frequency of clinic visits, and average time between clinic visits was consistent with the multivariate Cox proportional hazard results. I then ran a CD4 count submodel to assess the effect size of this biological predictor. Results show that the effect size for CD4 count was the highest of the socio-demographic and structural predictors. The odds of virologic resistance were increased by a factor of 43.06 (95% CI: 26.34–70.40) for patients with CD4 count slope <-10 compared with >5 CD4 count slope (holding all else constant).

I used an ROC analysis to assess the predictive power of the socio-demographic, structural, and CD4 count submodels. The socio-demographic submodel had the lowest predictive power (AUC=0.57), followed by the structural (AUC=0.77) and the CD4 count submodels (AUC=0.77). The AUC results for each of the submodels suggest that the structural and CD4 count submodels share the same predictive power, even though the change in CD4 count (per month) has a substantially larger odds ratio.[7] In this respect, the ROC analysis should be seen as validating the submodel estimates by comparing the ratio of the observed virologic failure outcomes with the classification of the predicted probabilities for each submodule into the low, medium, or high risk groups, as explained in greater detail in Section 6.4.3 of this chapter.

I the AUC of an ROC graph to make the final model selection. The final model included the following predictors: CD4 slope, age, male, proportion of time employed, migrated outside of study area, changed clinic since treatment initiation, number of clinic visits,

[7] The size of this odds ratio is also largely dependent on how the categories for the patient-specific CD4 count slopes have been determined, specifically the reference category.

duration on treatment, and the average time between clinic visits. The final model had an AUC of 0.856, which shows that the inclusion of certain socio-demographic and structural variables can improve the predictive performance of this model when compared with a model that includes only CD4 count, age, and sex. In this respect, the analyses presented in this chapter shows that societal level factors, such as the socio-demographic or structural variables, along with CD4 count monitoring, can be used to facilitate the detection of imperfect ART adherence. However, there is debate as to which method can best detect treatment response and adherence in resource-poor settings. Some researchers have argued that CD4 count monitoring, along with other clinical monitoring strategies (e.g., assessing patient symptoms) lacks the sensitivity to adequately detect virologic failure, and hence may not be an appropriate measure to determine if a patient is not adhering to his or her treatment schedule (Reynolds et al., 2009; Soria et al., 2009; Hoffmann et al., 2009). These researchers have argued that viral load monitoring alone should be the standard to determine poor adherence. However, this method of monitoring is expensive and may not be feasible in resource-limited settings, such as the Hlabisa study area, where a single viral load test is five times the price of a CD4 count test (NHLS, 2013).

I continue to explore the issue of treatment adherence in the following chapter. Specifically, I extend the analysis undertaken in this chapter in two important ways. First, I draw from the results of submodel 2, which suggest that patient interaction with the health-care setting is an important component in ensuring ART adherence. This interaction implies a range of health-seeking behaviors that increase exposure to treatment monitoring, adherence counseling, and a constant supply of ART medications. The results of this chapter, supported by the findings of similar studies, make a strong case for the improvement of, and investment in, interventions that increase patient interaction with the treatment and care setting. Second, if the treatment clinic is a critical site for the improvement or mainenance of treatment adherence, then attention must be drawn to the cost-effective strategies that are available to monitor patient response to ART. In this chapter I have pointed to the potential use of patient information relating to socio-demographics and clinic interaction that can be used for this purpose. Overall, strategies to ensure reliable treatment monitoring at reasonable costing structures will ensure that poor adherence can be detected earlier,

thereby improving the long term response to ART and avoiding the costs of switching to second-line ART regimens. I turn to this topic in greater detail in the following chapter.

Chapter 7

The Diagnostic Performance and Cost-Effectiveness of Two Monitoring Strategies to Identify Poor ART Adherence

7.1 Introduction

In this chapter I continue to examine the topic of poor adherence to ART. This work follows from the analyses undertaken in Chapter 6, where I identified CD4 cell count and patient interaction with the clinic setting to be significantly associated with virologic failure. The central aim of this chapter is motivated by these findings in two important respects. First, the results from the previous chapter suggest that patient response to ART could be improved or maintained through increased exposure to adherence services, counseling support, and regular access to treatment supplies.[1] Second, frequent clinic visits could enable health-care providers to better monitor patient response to ART, thereby leading to the earlier detection of adherence issues and the subsequent modification of existing treatment options. I consider treatment monitoring to be an important public health-care strategy to keep patients on ART, and devote the remainder of the chapter to this topic as a result.

In the previous chapter, I showed that a decline in CD4 cell count was strongly associated with virologic failure, and suggested that diagnostic efforts to detect imperfect adherence should include at least one of the three WHO recommended monitoring strategies. Briefly,

[1] For example, health-care staff could help a patient to partner with a 'treatment buddy' in order to facilitate short-term adherence to ART (Thomson et al., 2014; Ramin and Pottie, 2013; Unge et al., 2010; Wouters et al., 2009).

the three monitoring strategies are: 1) the evaluation of clinical signs and symptoms according to WHO clinical stage (1–5) condition, 2) routine immunological monitoring (6–12 months) which requires CD4 cell count testing, and 3) routine monitoring (6–12 months) of patient viral load (VL). The WHO's *Consolidated Guidelines on the Use of Antiretroviral Drugs* recommend VL monitoring as the preferred method to diagnose and confirm treatment failure, although the authors of the document acknowledge that this recommendation is based on 'low-quality' evidence (WHO, 2013: 133). In the absence of routine VL monitoring, the Guidelines recommend the use of both clinical and immunological monitoring to diagnose treatment failure—a position based on 'moderate-quality' evidence.

In this chapter I assess two strategies—CD4 and VL monitoring—to detect poor or imperfect adherence to ART. More specifically, I assess the diagnostic performance and cost-effectiveness of both monitoring strategies in a decentralized primary health-care setting in the Hlabisa subdistrict of the KwaZulu-Natal province, South Africa. In resource limited settings, CD4 monitoring is often implemented because of its affordability. However, CD4 monitoring may not be as accurate as VL monitoring in detecting treatment failure. I discuss the advantages and disadvantages of both monitoring strategies in greater detail in 7.2. Importantly, I am interested in whether the poorer sensitivity/specificity of CD4 count monitoring will offset its advantage in affordability when compared with VL monitoring.

In Section 7.4.4, I review recent studies that have evaluated the cost-effectiveness of the clinical, immunological, and virological monitoring strategies. In general, cost effectiveness analyses are used to 'identify the optimal allocation of available resources to maximize health' (Eichler et al., 2004). Generally, budgetary constraints will not allow health-care systems to make resources available to everyone. For this reason, a systematic (rather than intuitive) approach is required to inform decisions that are made about the distribution or allocation of health-care resources. The concept of a 'threshold' therefore plays an important role in cost-effectiveness evaluations. Often, policy makers will make a technology or treatment available below—or ration access above—some 'acceptable threshold'. In this context, consideration is given to both the monetary cost and health gain achieved at a specific threshold. In this analysis, I rely heavily on the threshold concept to define and identify patients at risk (very-low, low, medium, high) of treatment failure, and compare the cost-effectiveness of the CD4 and VL monitoring strategies at different risk group thresholds.

In this analysis, I use genotypic resistance as a measure of treatment failure, and as a proxy for imperfect adherence to ART.[2] Genotypic resistance is a more accurate and robust method to detect treatment failure. Briefly, HIV has a high rate of replication and produces millions of copies of itself every day (Stott et al., 2012). Many of these copies go unchecked in the replication process, resulting in structural changes to the make-up of the virus over a short period of time. As a result, these mutations make HIV resistant to one or more ARV drugs in the patient's current regimen.[3] Importantly, ARVs must be present in the patient's system for resistance to occur, and therefore indicates that a patient is not taking his or her medications consistently.[4] Resistance issues are addressed by switching the patient to a second-line regimen, which consists of ARV drugs that are effective or active against the virus. However, switching to second-line regimens is expensive, limits future treatment options, and increases the probability that a patient will have a poor response to future regimens. Adherence to standardized and affordable first-line ART regimens is therefore of critical importance to the success of HIV treatment and care strategies in resource-limited settings.

In the Section 7.3, I develop and explain the predictive model to assess the diagnostic performance of the CD4 and VL monitoring strategies. The first component of this predictive approach is to use a fixed effects model to compute the change in a patient's CD4 and VL count over the last 6 months (since their resistance test or last clinic visit). Patients are then classified as being at very-low, low, medium, or high risk of genotypic resistance given their change in CD4/VL count over the last 6 months. The cut-points used to define the risk groups are determined by the AUC of an ROC graph, as demonstrated in the previous chapter. I then use two established measures in medical statistics—the positive predictive value (PPV) and the number needed to test (NNT)—in order to complete the predictive/diagnostic component of this analysis.

[2] In other words, I do not use the criteria for first two consecutive VL>1000 copies/ml to measure virologic failure, as I did in Chapter 6. A genotypic resistance test is expensive and undertaken in a laboratory, the details of which are outlined in Section 7.3.2.

[3] In fact, the patient may become resistant to a class of ARV drugs. For example, Non-Nucleoside Reverse Transciptease Inhibitors (NNRTIs) and Protease Inhibitors (PIs) target HIV at different stages in the replication cycle. For example, a patient who develops resistance to efavirenz (EFV) is also likely to be resistant to nevirapine (NVP), both of which are NNRTIs.

[4] Patients who have no history of ingesting their medications typically have elevated VL measurements >1000 copies/ml and test negative for genotypic resistance.

I then evaluate the cost-effectiveness of the CD4 and VL strategies under three different scenarios—testing high risk patients only, testing high and medium risk patients, and testing high, medium, and low risk patients. To achieve this task, I present an equation to determine the total dollar cost for each monitoring strategy by risk group scenario. The total cost is a function of 1) the amount required to test every patient twice in order to detect 1000 genotypic resistance cases, and 2) the amount associated with incorrectly switching patients to a second-line ART regimen for the minimum period of one year. The costing model relies mainly on the specificity, PPV, and NNT measures as discussed in greater detail in Sections 6.4.3 and 7.4.3.

As explained in Section 7.4.4, my work differs from recent analyses that have assessed the cost-effectiveness of the three WHO recommended monitoring strategies. These studies often use sophisticated mathematical modeling techniques that make large assumptions about the dynamic transition of the population under investigation—typically over a 5–20 year costing period. Further, these studies typically rely on external and population level data to inform model parameters, and have to account for long-term price inflation, as well as the age-adjusted mortality and disability of the local population, amongst many other variables. The calculations required to estimate the cost-effectiveness of monitoring strategies under this approach are often quite complex and elaborate (Sassi, 2006), and often are not evaluated for their sensitivity (Fox-Rushby and Hanson, 2001).

In this study I present an analysis that uses simpler statistical methods and relies on observed, clinical data. This analysis is based on the idea that the cost-effectiveness of a specific monitoring strategy is a function of its predictive performance. For a given threshold, the health gain of a monitoring strategy is reflected by the proportion of patients correctly identified to have treatment failure. Having identified these patients, they would then be switched to second-line regimens in order re-suppress viral load and improve their health and survival outcomes. Further, the cost of given monitoring strategy is likely to increase if its diagnostic or predictive performance is poor. This means that more patients will have to be tested to detect treatment failure, with an increased proportion of false positives resulting in the switching of patients to more expensive second-line regimens. My aim in this chapter is to present a statistical analysis that will be informative in terms of the cost and health-gains achieved at specific thresholds and by monitoring strategy.

7.2 Background

A substantial body of research has shown that combination antiretroviral therapy (ART) can prevent the onward transmission of HIV (Cohen et al., 2011; Tanser et al., 2013; Baggaley et al., 2013), and dramatically improve the health and survival outcomes of HIV-infected patients (Ford et al., 2010; Nachega et al., 2013). In recent years, the development of standardized and affordable first-line drug regimens has resulted in the scale up of ART to more than six million people in sub-Saharan Africa (UNAIDS, 2012a). The monitoring of patient response to ART will now be crucial to the effectiveness of HIV treatment and care programs in this context (Hamers et al., 2012a). Monitoring strategies can be used to determine if treatment is successful and to identify or improve patient adherence. Research has shown that imperfect adherence to first-line ART is a primary determinant of treatment failure and acquired drug resistance (Ford et al., 2010; Wilson et al., 2009; Orrell et al., 2007; Nachega et al., 2007; Paterson et al., 2000; Bangsberg et al., 2000; Manasa et al., 2013). Switching patients to second-line ART regimens is expensive, increases the probability of treatment failure, and therefore limits future treatment options (Barth et al., 2012; Hosseinipour et al., 2009; Bartlett and Shao, 2009).

Three monitoring strategies are recommended by the WHO's *Consolidated Guidelines on the Use of Antiretroviral Drugs*. These are: 1) the evaluation of clinical signs and symptoms according to clinical stage (1–5) condition, 2) the routine monitoring of CD4 count (6–12 months), and 3) the routine monitoring of HIV-1 RNA viral load (VL) (6–12 months). The Guidelines recommend VL monitoring as the preferred method to diagnose and confirm treatment failure, although this recommendation is based on 'low-quality' evidence (WHO, 2013: 133). Clinical and CD4 monitoring are recommended in the absence of routine VL monitoring, although research has shown that these two strategies have a poorer sensitivity and specificity in detecting treatment failure (Hamers et al., 2012b; Gupta et al., 2009; Keiser et al., 2011; Reynolds et al., 2012; Rawizza et al., 2011; Reynolds et al., 2009; Castelnuovo et al., 2009; Soria et al., 2009; Mee et al., 2008; Moore et al., 2008). Decreased specificity is likely to result in the unnecessary switching of patients who have virologic suppression to more expensive second-line ART regimens (Sigaloff et al., 2011). However, it may not be economically feasible to implement VL monitoring because of the higher cost

of the assay, the technical complexity of the test, and the logistics required to transport the samples to centralized laboratory facilities (Estill et al., 2013; Roberts et al., 2012; Kahn et al., 2011). Decision-makers in public health-care facilities will therefore need to consider the diagnostic vs. cost trade-off as treatment monitoring strategies are implemented across resource-limited settings.

In this chapter I evaluate the predictive performance and cost-effectiveness of two strategies—CD4 and VL monitoring—to poor patient response to ART. The study is based in a decentralized public health-care setting in KwaZulu-Natal, South Africa, where HIV treatment and care services are provided at no cost to enrolled patients. I specifically determine the dollar cost to detect 1000 genotypic resistance cases for each monitoring strategy, which is the sum of 1) the amount needed to undertake baseline CD4 or VL testing, and 2) the amount associated with incorrectly switching patients to a more expensive second-line ART regimen for the duration of a year. This analysis is based on the idea that the cost-effectiveness of a specific monitoring strategy is a function of its predictive performance. Ultimately, the cost-effectiveness model presented here will enable me to assess whether the affordability of CD4 baseline testing is offset by its poorer specificity when compared with VL monitoring.

7.3 Methods

7.3.1 Study setting

The Hlabisa HIV Treatment and Care Programme is located in the Umkhanyakude district of the northern KwaZulu-Natal province. Established in 2004 by the South African Department of Health and the Africa Centre for Health and Population Studies, the program provides ART free of charge to HIV-infected patients using standard South African and WHO treatment guidelines (Lessells et al., 2013). HIV services are provided primarily by nurses and counselors across 17 primary health-care clinics and one district hospital within the study area. Between 2004 and early 2010, first-line ART regimens consisted of stavudine (d4T), lamivudine (3TC), and either efavirenz (EFV) or nevirapine (NVP). In 2010, tenofovir (TDF) replaced d4T in first-line regimens and was available for substitution in the presence of AZT toxicity. The demographic characteristics of the study setting and HIV

program are described in greater detail elsewhere (Vandormael et al., 2014; Tanser et al., 2008; Houlihan et al., 2011).

7.3.2 Study design

The study is a longitudinal cohort design enrolling patients from HIV Treatment and Care Programme between January 2006 and early January 2014. Patient information was collected using a standardized clinical form and entered into the Africa Centre's ART Evaluation and Monitoring System (ARTemis). I used the ARTemis database to identify all adults ($\geq$18 years) on a first-line ART regimen for more than 6 months. All patients underwent routine CD4 and VL testing. CD4 tests were scheduled on a 6 month basis (Houlihan et al., 2011). Prior to 2010, VL tests were scheduled every six months and repeated after three months if VL was >5000 copies/ml. From 2010 onwards, VL tests were scheduled at month 6 and month 12, and then every 12 months if VL remained <400 copies/ml. A VL >1000 copies/ml resulted in a repeat measurement at three months (Manasa et al., 2013).

Treatment failure was identified through genotypic resistance testing. Resistance testing was undertaken using the following criteria: Patients with latest VL >1000 copies/ml were identified by clinic staff during routine visits and referred to a physician for review, or were proactively identified, contacted by program staff, and booked for a physician review. Only patients with indications of virologic failure were therefore sent and tested for genotypic resistance. A 5 ml blood sample was collected during the clinical evaluation, and an in-house HIV-1 drug resistance genotyping method was used to evaluate the samples, as previously described (Manasa et al., 2013). A genosusceptibility score (GSS) for each antiretroviral (ARV) agent in the first-line regimen was determined using a Rega 8.0.0.2 algorithm. The scores for each agent were totaled, with a GSS <2 indicating genotypic resistance. Patients not sent for a resistance test, who had no VL >400 copies/ml 30 days after ART initiation, or had a GSS $\geq$2 were defined as not having treatment failure. Clinical information for patients undergoing genotype testing was entered into the SATuRN REGA database (de Oliveira et al., 2010).

7.3.3 Ethics statement

The study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal and the Health Research Committee of the KwaZulu-Natal Department of Health. Written informed consent was obtained from all the study participants

7.4 Statistical analysis

I selected all CD4 and VL test measurements 30 days after the date of ART initiation until the genotype test date or the last clinic visit date. The baseline was defined as the most recent CD4 and VL measurement prior to the exposure start date, which I also included in the analysis. I carried forward any CD4 measurements for 180 days and VL measurements for 90 days, and then interpolated the remaining missing values between tests dates no greater than 12 months. I transformed all VL measures onto the $\log_{10}$ scale. Only patients with a baseline count followed by at least one CD4 or VL measurement were included in the analysis.

7.4.1 Predictive/diagnostic model

The following statistical procedures were undertaken to develop the predictive/diagnostic model.

Step 1: Fixed effects model. First, I obtained patient-specific estimates for the mean change in CD4 and VL count using a fixed effects model. The model is:

$$y_{ij} = \beta_{0j} + \beta_{1j}x_{ij} + \epsilon_{ij}, \quad i = 1, \ldots, n_j;\ j = 1, \ldots, m \tag{7.1}$$

where for the jth patient: β_{0j} is the CD4/VL count at baseline ($i = 1$), β_{1j} is the monthly rate of change in CD4/VL count, x_{ij} represents the number of months between the test date (time point $= i$) and baseline date, and ϵ_{ij} is the ith statistical error.

I then computed a relative percentage change in patient CD4 count using the predicted values obtained from the individual fixed effects model (equation 7.1) at the date of the genotype test or last clinic visit ($i = 2$) and six months prior to this date ($i = 1$). The predicted values were obtained with:

$$\tilde{y}_{ij} = \hat{\beta}_{0j} + \hat{\beta}_{1j}x_{ij}, \quad i = 1, 2;\ j = 1, \ldots, m \tag{7.2}$$

where for patient j: $\tilde{y}_{ij}$ is the point prediction (at time-point $i = 1, 2$), $\hat{\beta}_{0j}$ and $\hat{\beta}_{1j}$ is the estimated intercept and slope respectively, x_{2j} is the duration of exposure to ART, and x_{1j} is the duration of exposure less 6 months. The relative percentage change in a patient's predicted CD4 count over the last 6 months, abbreviated to pCD4 (6mo), was computed as follows:

$$\text{pCD4 (6mo)}_j = \frac{\tilde{y}_{2j} - \tilde{y}_{1j}}{\tilde{y}_{1j}} \times 100. \tag{7.3}$$

I computed each patient's absolute change in predicted $\log_{10}$VL over the last 6 months, abbreviated to aLVL (6mo):

$$\text{aLVL (6mo)}_j = \tilde{y}_{2j} - \tilde{y}_{1j}. \tag{7.4}$$

The percentage change in CD4 and absolute log change in VL could also be computed using the two most recent observed measurements across a six month period, as was done in Hoffmann et al. (2013). I justify the use of a fixed effects model because a) all patient CD4 and VL measurements since exposure to ART are used, and b) to produce estimates that are less sensitive to large variations between two successive CD4 or VL measurements over the six month period.

Step 2: Define the risk groups. I then classified patients as having a very-low, low, medium, or high risk of genotypic resistance based on their pCD4 (6mo) or aLVL (6mo) estimates. The classification model for the pCD4 (6mo) estimates was determined by the step function:

$$\text{Risk group} = \begin{cases} \text{very-low} & \text{if } \text{pCD4 (6mo)} > z \\ \text{low} & \text{if } y > \text{pCD4 (6mo)} \leq z \\ \text{medium} & \text{if } x \geq \text{pCD4 (6mo)} \leq y \\ \text{high} & \text{if } \text{pCD4 (6mo)} < x, \end{cases} \tag{7.5}$$

where $x < y < z$, and (x, y, z) are variables taking on real values called cut-points. The classification model for the aLVL (6mo) estimates was similarly determined:

$$\text{Risk group} = \begin{cases} \text{very-low} & \text{if aLVL (6mo)} < x \\ \text{low} & \text{if } x \geq \text{aLVL (6mo)} < y \\ \text{medium} & \text{if } y \geq \text{aLVL (6mo)} < z \\ \text{high} & \text{if aLVL (6mo)} \geq z, \end{cases} \tag{7.6}$$

where $x < y < z$. The cut-points, which define the risk group categories, are derived from the maximum area under the curve (AUC) of a receiver operating characteristics (ROC) graph, as explained in greater detail in Section 6.4.3. For example, the cut-points $(x = 0\%, y = 5\%, z = 20\%)$ would classify patient pCD4 (6mo) <0% as high risk, patient pCD4 (6mo) between 0–5% as medium risk, patient pCD4 (6mo) between 5.1–20% as low risk, and patient pCD4 (6mo) >20% as a very-low risk of genotypic resistance. To validate the predictive model, I perform a logistic regression model to assess the association between the genotypic resistance outcome and the CD4 and VL risk groups separately (adjusting for age, sex, and duration of virologic failure). I then plotted the time to genotypic resistance for the low, medium, and high risk groups using Kaplan-Meier survival curves.

7.4.2 Performance of the predictive model

I first demonstrate how the predictive performance of the CD4 and VL monitoring strategies are evaluated using example cut-points with toy data. Table 7.1 shows a confusion matrix for the four risk groups, where all patients with a pCD4 (6mo) <0% are classified as high risk, etc. (see the above section).

Resistance	Very-low Risk	Low Risk	Medium Risk	High Risk	Total
No	315	2,137	749	165	3,366
Yes	6	76	178	137	397
Total	321	2,213	927	302	3,763

Table 7.1: Confusion matrix showing toy data for pCD4 (6mo) risk groups

I use the confusion matrix to obtain the sensitivity, specificity, positive predictive value (PPV), and the number needed to test (NNT) for each risk group. I demonstrated the calculation of the sensitivity and specificity measures in greater detail in Section 6.4.3 of the dissertation; I briefly demonstrate the calculation of the PPV and NNT measures in this section. The PPV is defined as the number of true positives detected of the total (true and false) positives classified. Or more specifically, it is the number of patients that test positive for genotypic resistance divided by the total number of patients classified as having genotypic resistance for a given risk group. Using the example data presented in Table 7.1, the PPV for the high risk group is:

$$\text{PPV} = \frac{\text{number of true positives}}{\text{number of true positives} + \text{number of false positives}} = \frac{137}{302} \times 100 = 45\%.$$

For the high risk group, the sensitivity and PPV measures share the same numerator (137), but differ in the denominator—the PPV denominator is 302 and the sensitivity denominator is 397 (i.e., the total number of patients that tested positive for genotypic resistance). The PPV is the inverse of the NNT, which represents the number of patients that must be tested in order to detect one true positive case of genotypic resistance. The ideal NNT is 1, with a higher NNT indicating a less effective diagnostic strategy (Laupacis et al., 1988). For our example, the NNT is computed as $1/\text{PPV} = (137/302)^{-1} = 2.2$, which gives the number of high risk patients that need to be tested to detect one treatment failure case. The NNT can be multiplied by the dollar amount for a single CD4 or VL test.

7.4.3 Cost-effectiveness model

In this section I present a model with which to evaluate the cost-effectiveness of the CD4 and VL monitoring strategies. My aim is to estimate a single dollar amount for both strategies under three scenarios (or thresholds). The three scenarios are:

Scenario A: Test high risk patients only,

Scenario B: Test high and medium risk patients,

Scenario C: Test high, medium, and low risk patients.

For each combination of strategy and scenario ($n = 6$), the dollar amount reflects the sum of two different costs. The first is the baseline cost needed to test patients twice using

a CD4 or VL test; and the second is the cost associated with incorrectly switching patients to a more expensive second-line regimen for the duration of a year.

Let Λ be the total cost for the CD4 and VL monitoring strategies separately under Scenario A, B, and C. Let α be the number of patients that need to be tested to detect the first 1000 genotypic resistance cases. Let η be the false positive rate, and let δ be the difference in annual cost between a first-and second-line ART regimen. Then, the total cost for each monitoring strategy under Scenario A, B, or C is:

$$\begin{aligned} \Lambda_{ij} &= \alpha_{ij} + (\beta_{ij} \times \delta) \\ &= 2(\kappa_{ij} t_i) + (\kappa_{ij} \eta_{ij} \times \delta), \end{aligned} \tag{7.7}$$

where i indexes the CD4 or VL monitoring strategy and j indexes the three scenarios.

- For each scenario (and ignoring subscripts), I define α as the baseline cost to test each patient twice. I expand α to $2(\kappa t)$, where κ is the total number of patients that need to be tested to determine the first 1000 genotypic resistance cases (thus $\kappa = \text{NNT} \times 1000$). κ is then multiplied by t, which represents the cost of a single CD4 count test ($9.18) or a VL test ($45.88) at a primary health care clinic in South Africa (NHLS, 2013).
- I define β as the number of patients that would have been incorrectly switched to a second-line ART regimen under each scenario. β is derived from the false positive rate η which is calculated as $1 - s$, where s is the specificity expressed as a proportion. η is therefore multiplied by κ, the total number of patients tested to detect 1000 genotypic resistance cases, in order to arrive at the number of patients incorrectly identified to have genotypic resistance (and who would therefore be switched to a second-line regimen).
- I define δ as $319, the difference between the annual cost of a first-line regimen ($146.50) and a second-line regimen ($465.50) at public health-care clinics in South Africa (Estill et al., 2013).

To demonstrate the costing model, I compute the total cost for the CD4 monitoring strategy in Scenario A (test high risk patients only) and the information from Table 7.6:

$$\alpha = 2(\kappa t) = 2(2200 \times \$9.18) = \$40,392$$
$$\beta = \kappa\eta = 2200 \times 0.049 = 107.8$$
$$\delta = (\$465.50 - \$146.50) = \$319, \text{ and}$$
$$\Lambda = \alpha + (\beta \times \delta) = \$74,780$$

Some notes that can be made about this cost-effectiveness model:

1. Patients are tested twice to simplify the comparisons between the monitoring strategies, and because a minimum of two measurements are required to compute a change in CD4 or VL count over a given time period.

2. The cost to switch patients to second-line regimens who have been correctly identified to have genotypic resistance is a constant for both monitoring strategies by scenario, and is therefore not factored into the costing equation. Since I represent the dollar amount to detect 1000 genotypic resistance cases, the constant represents a cost of $1000 \times \delta$ for all monitoring strategy–scenario combinations.

3. The total dollar amount does not include the cost of a patient's current first-line regimen, which is a constant under all monitoring-scenario combinations.

4. The cost of incorrectly switching a patient to a second-line regimen is computed for the duration of a year, represented by $\beta \times \delta$. It is possible to compute the cumulative cost over a 5-year period or longer adjusting for price inflation.

5. The model does not factor the logistical costs associated with implementing VL laboratory equipment and facilities, staff training, and other associated costs. The cost-effectiveness analysis presented here is concerned specifically with the diagnostic or predictive component of CD4 and VL monitoring in resource-limited settings. The additional cost of introducing laboratory facilities may influence the decision to implement VL monitoring, a factor that is not considered in the costing model.

7.4.4 Review of alternative cost-effectiveness analyses

As mentioned in Section 7.1 of this chapter, a cost-effectiveness studies often rely on a threshold estimate, which is a rate expressing the monetary cost and the health gain for a given monitoring program. Quality Adjusted Life Years and Life Years Saved (LYS) are two popular measures that reflect the health gain component (the denominator) of a threshold estimate, whereas DALYs reflect a health loss (Eichler et al., 2004). More specifically, DALYs are the sum of the present value of future years of lifetime lost through premature mortality (YYL), and the present value of years of future life-time adjusted for the average severity of a particular disability (YLD) (Fox-Rushby and Hanson, 2001). For example, the YLL is the time from death to the expected age at which that person was expected to live; and the YDL is the time experiencing severe morbidity. One DALY is equal to one year of healthy life lost. In terms of the cost-effectiveness of WHO recommended monitoring strategies, the number of DALYs averted reflects the difference between DALY computed for a person undergoing a more effective monitoring strategy and the standard monitoring strategy.

A review of the literature shows that a large proportion of studies use QALYs (Estill et al., 2013; Kahn and Marseille, 2013; Phillips et al., 2008), DALYs (Braithwaite et al., 2014; Kahn et al., 2011; Keebler et al., 2014; Lara et al., 2012; Sempa et al., 2013; Marseille et al., 2012) or LYS (Boyer et al., 2013; Bendavid et al., 2008) measures over a specified time period to undertake the cost-effectiveness of the three ART monitoring strategies. The majority of these studies cited use the incremental cost effectiveness ratio (ICER), which is the difference in the cost between two monitoring options divided by the difference in QALYs/DALYs/LYS. For mutually exclusive programs (i.e., a control or treatment arm), an incremental cost effectiveness ratio (ICER) is used to compare the cost-effectiveness of a each intervention with the next most effective option. In their analysis, for example, Kahn et al. (2011) assess the cost and health value for each incremental use of resources to monitor patient response to ART. Their method reflects the differences in costs per person-year for the monitoring tests themselves; a difference in costs of antiretroviral regimens; and out/in-patient care. They also projected costs of future HIV care for 15 years.

The equations to compute QALYs are presented in Sassi (2006) and DALYs are presented in Murray (1994) and Murray and Lopez (1996). The computation of DALYs require many

assumptions relating to the weights for life expectancy, age, future time, and disability (Fox-Rushby and Hanson, 2001). For this reason, data on cohort life expectancy, age specific mortality rates, and country or region specific life tables are required (Sassi, 2006). Disability weights necessary for the computation of the YDL measure and are sometimes derived from the Global Burden of Disease project (Mathers et al., 2008). Further, in an ideal scenario, the total DALYs would be computed as the sum of person-specific DALYs. In reality, the calculations are made from the population level and require a number of assumptions relating to the proportion of the population monitored, and so on. For this reason, mathematical models are often invoked to compute QALYs/DALYs using observed data from existing projects to inform the parameter settings (Estill et al., 2013; Keebler et al., 2014; Phillips et al., 2008; Braithwaite et al., 2011).

My work differs from these studies, which often use sophisticated mathematical modeling techniques that are dependent on large assumptions about the dynamic transition of the population under investigation—typically over a 5–20 year costing period. Further, these studies typically have to account for long-term price inflation amongst many other variables. The calculations required to estimate the cost-effectiveness of monitoring strategies under this approach are often quite complex and elaborate (Sassi, 2006), and often are not evaluated for their sensitivity (Fox-Rushby and Hanson, 2001). I present a straightforward cost-effectiveness model that relies on observed/clinical data, and that use techniques that are common in the field of medical statistics. Here, I obtain the health gain component for a given threshold as a function of the PPV, and the cost component as a function of the specificity, of the predictive model.

7.5 Results

A total of 5596 patients $\geq$18 years of age and on ART for at least 6 months were eligible for this study. Of these eligible patients, 493 were referred for a genotypic resistance test: 397 patients tested positive for genotypic resistance with a GSS $<$2, and thus identified as having treatment failure. Patients with a GSS $\geq$2 ($n = 83$) remained in the study and were identified as not having treatment failure. There were 5103 patients that were not considered as candidates for a genotypic resistance test. Of these, 3283 had virologic suppression $<$400 copies/ml. I dropped 1112 patients that had one or more VL $\geq$400 copies/ml and 708

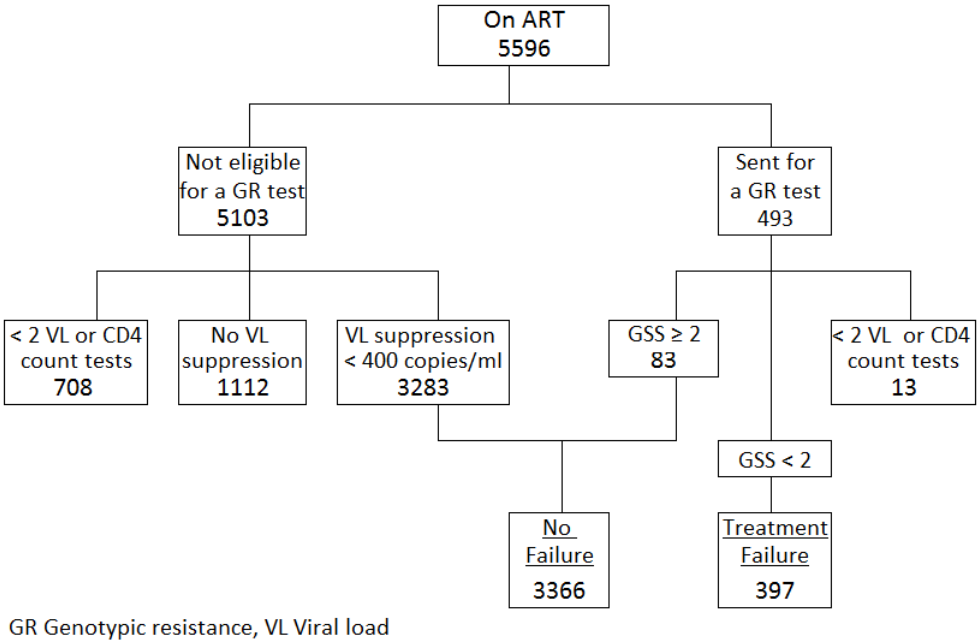

Figure 7.1: Data flow diagram of eligible patients (≥18 years) on ART for 6 or more months that were included in the study

patients that had either less than two CD4 or VL counts in total (including the baseline measure). The final analytic sample consisted of 3763 patients. The data flow diagram is shown in Figure 7.1.

The mean age of the cohort was 40.8 (sd = 10.5) years and there were 965 (25.6%) men. The mean duration of ART exposure (30 days after the date of cART initiation to the genotypic resistance test or last clinic visit date) was 49.6 (sd = 23.2) months, and the average time between test dates was 8.01 (sd = 3.03) months. At baseline, the median CD4 count was 150 (IQR = 82–206) cells/µl and the median VL count was 40 (IQR = 25–11000) copies/ml. The fixed effect CD4 slopes had a median of 7.4 (IQR = 3.9–12.3) cells/µl change per month, and the fixed effect VL slopes had a median of log −0.03 (IQR = −0.06–0.00) copies/ml change per month. The distributions for the CD4 and VL fixed effects (slopes) are shown in Figures 8.5 and 8.6 of the Appendix.

7.5.1 Risk group cut-points

I used the AUC of an ROC graph to determine the risk group cut-points. The cut-points ($x = 0\%, y = 5\%, z = 20\%$) for the pCD4 (6mo) estimates were derived with an AUC of 0.79; Figure 7.3 displays the AUC and ROC graph used to construct the risk groups. Patients were classified as having a very-low (pCD4 (6mo) >20%), low (pCD4 (6mo) between 5.1–20%), medium (pCD4 (6mo) between 0–5%), or high risk (pCD4 (6mo) <0%) of genotypic resistance. Table 7.2 shows the number of patients with genotypic resistance classified under the four risk groups. The cut-points for the aLVL (6mo) estimates were ($x = -0.3, y = 0, z = 0.3$) for the aLVL (6mo) estimates, with an AUC of 0.87; Figure 7.3 displays the AUC and ROC graph used to construct the risk groups. Patients were classified as having a very-low (aLVL (6mo) <-0.3), low (aLVL (6mo) between -0.3–0), medium (aLVL (6mo) between 0.01–0.3), and high risk (aLVL (6mo) >0.3) of genotypic resistance. Table 7.3 shows the number of patients with genotypic resistance classified under the four risk groups.

	Very-low Risk		Low Risk		Medium Risk		High Risk		Total	
Resistance	No.	%	No.	%	No.	%	No.	%	No.	%
No	315	98.1	2,137	96.6	749	80.8	165	54.6	3,366	89.4
Yes	6	1.9	76	3.4	178	19.2	137	45.4	397	10.6
Total	321	100.0	2,213	100.0	927	100.0	302	100.0	3,763	100.0

Table 7.2: Confusion matrix showing the classification schema for pCD4 (6mo) risk groups

	Very-low Risk		Low Risk		Medium Risk		High Risk		Total	
Resistance	No.	%	No.	%	No.	%	No.	%	No.	%
No	1,418	98.5	1,757	95.7	125	42.5	66	34.2	3,366	89.4
Yes	22	1.5	79	4.3	169	57.5	127	65.8	397	10.6
Total	1,440	100.0	1,836	100.0	294	100.0	193	100.0	3,763	100.0

Table 7.3: Confusion matrix showing the classification schema for aLVL (6mo) risk groups

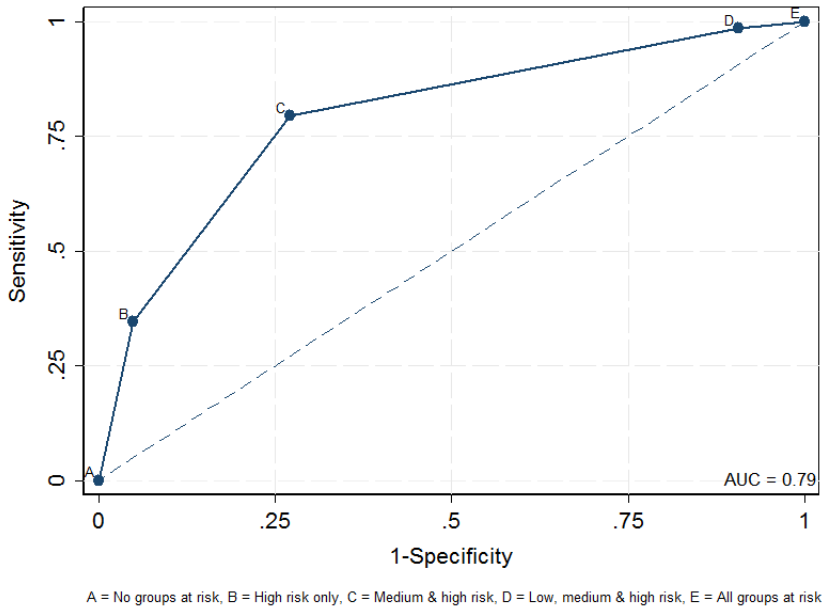

Figure 7.2: ROC graph showing risk groups to classify pCD4 (6mo) estimates

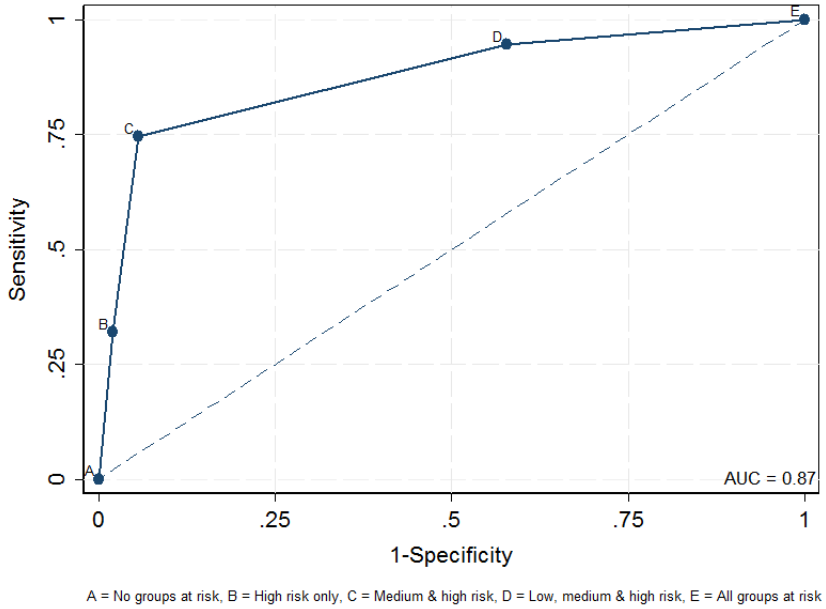

Figure 7.3: ROC graph showing risk groups to classify aLVL (6mo) estimates

7.5.2 Models of association

Logistic regression: I used a logistic regression model to assess the association between the risk group categories and the odds of genotypic resistance. Table 7.4 shows that the univariate associations are large and statistically significant: the odds of genotypic resistance for high risk patients (i.e., a pCD4 (6mo) estimate <0%) is increased by a factor of 43.01 (95% CI: 18.59–99.53), compared with very-low risk patients (i.e., a pCD4 (6mo) estimate >20%). The multivariate model (Table 7.4) shows the odds for the added sex, and age covariates for the CD4 risk groups. There is no significant difference between the very-low and low risk groups once adjusting for the covariates. Holding all else constant, the odds of genotypic resistance for high risk patients is increased by a factor of 55.52 (95% CI: 23.80–129.51), compared with very-low risk patients.

	Univariate			**Multivariate**		
	OR	**(95% CI)**	**p-value**	**OR**	**(95% CI)**	**p-value**
CD4 Count:[a]						
Very-low risk	Ref.			Ref.		
Low risk	1.87	(0.81–4.32)	0.145	2.33	(1.00–5.40)	0.050
Medium risk	12.48	(5.47–28.44)	0.000	16.99	(7.40–39.02)	0.000
High risk	43.01	(18.59–99.53)	0.000	55.52	(23.80–129.51)	0.000
Age[b]				0.59	(0.52–0.67)	0.000
Male				1.15	(0.88–1.49)	0.306
Constant	0.02	(0.01–0.04)	0.000	0.11	(0.05–0.28)	0.000
Log VL:[d]						
Very-low risk	Ref.			Ref.		
Low risk	2.90	(1.80–4.67)	0.000	2.85	(1.77–4.60)	0.000
Medium risk	87.14	(53.90–140.88)	0.000	88.19	(54.32–143.16)	0.000
High risk	121.21	(72.43–202.85)	0.000	118.12	(70.19–198.77)	0.000
Age[b]				0.66	(0.57–0.76)	0.000
Male				1.47	(1.08–2.00)	0.015
Constant	0.02	(0.01–0.02)	0.000	0.07	(0.04–0.14)	0.000
N	3763			3763		

[a]Relative percentage change in CD4 count over 6 months [b]10 year increase

[d]Absolute change in $\log_{10}$VL over 6 months

Table 7.4: Logistic regression output for the CD4 and VL risk group categories

Table 7.4 shows large associations between the VL risk groups and the odds of genotypic resistance. The odds are increased by a factor of 121.21 (95% CI: 72.43–202.85) for high risk patients (i.e., an aLVL (6mo) estimate >0.3), compared with a very-low risk group (i.e, an aLVL (6mo) estimate <−0.3). Younger patients and men are more likely to have genotypic resistance, holding all else constant.

	Univariate			Multivariate		
	HR	**(95% CI)**	**p-value**	**HR**	**(95% CI)**	**p-value**
CD4 Count[a]	1.13	(1.11–1.14)	0.000	1.12	(1.11–1.14)	0.000
Age[b]				0.57	(0.51–0.64)	0.000
Male				0.99	(0.79–1.24)	0.954
Log VL	3.17	(2.97–3.39)	0.000	3.10	(2.90–3.31)	0.000
Age				0.96	(0.95–0.97)	0.000
Male				1.15	(0.93–1.44)	0.200
N	3763			3763		

[a]For a 20 cell count decrease in CD4 [b]10 year increase

Table 7.5: Cox proportional hazard results for CD4/VL measures and covariates

Survival analysis: I undertook a Cox proportional hazards model to validate the association between the CD4/VL measures and genotypic resistance. I included the raw CD4 and $\log_{10}$VL measures as time-varying predictors in the model, with the outcome variable defined as the time to genotypic resistance. Table 7.5 shows the univariate and multivariate results for CD4 count, age, and sex. For the univariate model, a 20 unit decrease in CD4 cell count is associated with a 1.12 (95% CI: 1.11–1.14) increase in the hazard of genotypic resistance. Multivariate results shows that the hazard of genotypic resistance is associated with younger patients, holding all else constant. Table 7.5 shows that a one unit increase in $\log_{10}$VL is associated with a 3.10 (95% CI: 2.90–3.31) increase in the hazard of genotypic resistance, holding all else constant. Figures 7.4 and 7.5 show the Kaplan-Meier survival curves by CD4 and VL risk groups respectively.

7.5.3 Predictive model

I assess the predictive performance for the CD4 and VL monitoring strategies under three scenarios: Scenario A (test high risk patients only), Scenario B (test high and medium

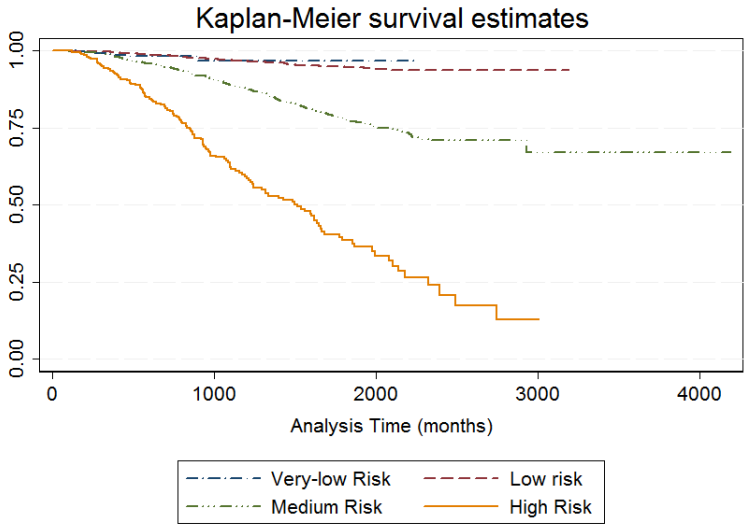

Figure 7.4: Kaplan-Meier survival curves by CD4 risk group

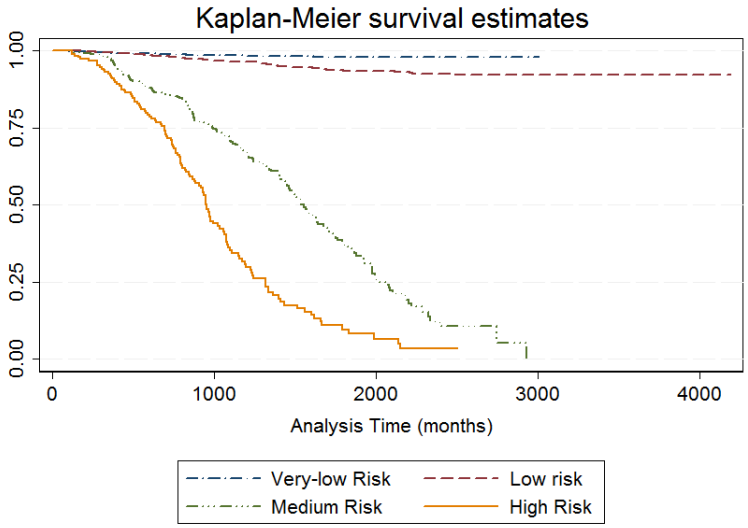

Figure 7.5: Kaplan-Meier survival curves by VL risk group

risk patients), and Scenario C (test high, medium, and low risk patients). For the CD4 monitoring strategy, the three scenarios equate to testing all patients with a pCD4 (6mo) <0% (Scenario A), <5% (Scenario B), and <20% (Scenario C). For the VL monitoring strategy, the three scenarios equate to testing all patients with a aLVL (6mo) >0.3 (Scenario A), >0 (Scenario B), and >-0.3 (Scenario C).

The results are shown in Table 7.6. For the CD4 monitoring strategy: of the 397 patients that tested positive for genotypic resistance (GSS <2), 137 were correctly classified as having genotypic resistance under Scenario A, giving a sensitivity of 34.5% and a specificity of 95.1%. Scenario B shows a higher sensitivity (79.3%) but lower specificity (72.8%) with the testing of medium and high risk patients, when compared with Scenario A. Testing low, medium, and high risk patients under Scenario C gives the highest sensitivity of the three scenarios (98.5%), but with the lowest specificity (9.4%).

There were 302 patients classified to have genotypic resistance under Scenario A. Of these patients, 137 tested positive for genotypic resistance, giving a PPV of 45.4% (Table 7.6). For Scenario A, 2.2 patients would have to be tested to detect one genotypic resistance case; and the cost to detect one positive case would be $2.2 \times \$9.18 = \$20.2$. Of the three scenarios, Scenario A would be the most cost-effective to detect one genotypic resistance case, however, it would miss 65.5% of the patients that truly have genotypic resistance. Scenario B misses less positive cases (20.7%), but has a lower PPV (25.6%) compared with Scenario A, and therefore a higher cost ($35.8) to detect one positive case. Scenario C misses the least number of genotypic resistance cases (1.5%) but is the most costly at $80.8 to detect one genotypic resistance case.

Table 7.7 shows the results for the VL monitoring strategy. Of the three scenarios, testing high risk patients only under Scenario A gives the poorest sensitivity (32%), but the highest specificity (98%) and PPV (65.8%), and the lowest NNT (1.50) and cost to detect one genotypic resistance case ($68.8). The sensitivity is increased to 74.6% under Scenario B, with a slight decrease in specificity (94.3%). The NNT is 1.60 and the cost to detect one genotypic resistance case is $73.4. Scenario C is the least cost-effective in detecting one genotypic resistance case ($285) given an NNT of 6.2. However, only 5.5% genotypic resistance cases are missed under Scenario C. The cost to detect one genotypic resistance case is substantially higher under the three scenarios compared to CD4 monitoring.

Scenario	**A**	**B**	**C**
pCD4 (6mo) Threshold	<0%	<5%	<20%
N	302	1,229	3,442
Genotypic resistance (GR) *N*	137	315	391
No genotypic resistance *N*	165	914	3,051
Sensitivity (%)	34.5	79.3	98.5
Specificity (%)	95.1	72.8	9.4
Missed genotypic resistance (%)	65.5	20.7	1.5
PPV (%)	45.4	25.6	11.4
Number needed to test (NNT)	2.2	3.9	8.8
Cost to detect one GR case ($)	20.2	35.8	80.8

AUC for this ROC analysis is 0.79

Table 7.6: Sensitivity, specificity, and NNT for CD4 risk groups

Scenario	**A**	**B**	**C**
aLVL (6mo) Threshold	>0.3	>0	>-0.3
N	193	487	2,323
Genotypic resistance (GR) *N*	127	296	375
No genotypic resistance *N*	66	191	1,948
Sensitivity (%)	32	74.6	94.5
Specificity (%)	98	94.3	42.1
Missed genotypic resistance (%)	68	25.4	5.5
PPV (%)	65.8	60.8	16.1
Number needed to test (NNT)	1.5	1.6	6.2
Cost to detect one GR case ($)	68.8	73.4	285

The AUC for this ROC analysis is 0.87

Table 7.7: Sensitivity, specificity, and NNT for VL risk groups

7.5.4 Cost-effectiveness model

In this section I report the total cost to detect 1000 genotypic resistance cases for the CD4 and VL monitoring strategies by risk group scenario. The results are shown in Figure 7.6. The cost to test high risk patients only under Scenario A using CD4 monitoring is $\$74,780$, compared with a cost of $\$147,210$ for VL monitoring. Under Scenario A, the difference in sensitivity between the two monitoring strategies is not substantially large (i.e., 34.5% vs. 42.1%). Indeed, the CD4 count monitoring strategy for Scenario A is substantially more cost effective and is comparable in sensitivity to the VL monitoring strategy. CD4 count monitoring is substantially more expensive than VL monitoring for Scenario B, when medium and high risk patients are tested. The cost for CD4 monitoring increases in Scenario B because of a higher NNT = 3.9 (vs. a Scenario A NNT = 2.2) and, more importantly, because of the higher percentage (27.2%) of the $\kappa = 3900$ patients incorrectly switched to a second-line regimen. The total cost for CD4 monitoring is therefore $\$409,999$ vs. the total cost of VL monitoring, which is $\$175,909$. Of the three scenarios, Scenario C is the least cost-effective because of the higher NNT for both the CD4 and VL monitoring strategies. The high NNT and poor specificity for CD4 monitoring in Scenario C results in a less cost-effective strategy when compared with VL monitoring.

7.6 Discussion

The virologic suppression of HIV is the most important indicator that a patient is responding well to ART (Nachega et al., 2007; Paterson et al., 2000; Bangsberg et al., 2000), and patients who have treatment interruptions are at greatest risk of HIV drug resistance (Meresse et al., 2014; Gupta et al., 2009). At the start of this chapter I argued that the monitoring of patient response to ART will be crucial to public health-care efforts to manage and treat HIV. Unfortunately, the successful implementation of effective treatment monitoring strategies is often constrained by the economic realities of resource-limited settings. In the case of VL monitoring, the requirement for expensive laboratory facilities and the cost of the test mean that this strategy is not easily implemented in decentralized health-care settings in rural South Africa.

Because of these economic constraints, CD4 monitoring is generally promoted as an affordable alternative to VL monitoring. However, concerns have been raised about the diagnostic performance of this monitoring strategy, as was discussed in Section 7.2. In this analysis, I specifically evaluate if the affordability of CD4 testing is offset by its poorer diagnostic performance (when compared with VL monitoring). For the cost-effectiveness model, I wanted to represent the predictive performance of CD4 count monitoring as a cost-benefit ratio in dollar terms. This dollar amount included a baseline cost to test patients twice based on the predictive positive value (PPV) and the cost associated with incorrectly switching patients to a second-line regimen (as measured by the specificity). My aim therefore was to evaluate both the CD4 and VL monitoring strategies on the bases of both their predictive and cost performance in identifying treatment failure.

Patients for this study were recruited from the HIV Treatment and Care Programme in the Hlabisa district of the KwaZulu-Natal province of South Africa. All patients in this study had at least 2 CD4 and VL measures, and were on first-line ART for six or more months. Patients with poor treatment response were identified and sent for a genotypic resistance test; patients with a GSS $<$ were defined as having drug resistance and hence treatment failure. Patients undergoing routine monitoring who had all VL $<$400 copies/ml were defined as not having treatment failure. I used a fixed effects analysis to obtain the relative percentage change in predicted CD4 count over six months, abbreviated to pCD4 (6mo), and the absolute change in predicted $\log_{10}$VL over six months, abbreviated to aLVL (6mo). These changes were then used to classify patients as being in a high, medium, low, or very-low risk group for genotypic resistance. Under three testing scenarios, I then obtained the sensitivity, specificity, positive predictive power (PPV), and the number needed to test (NNT) for each scenario by CD4 or VL monitoring strategy. Finally, I computed the dollar cost to detect 1000 genotypic resistance cases, a measure which is the sum of the amount needed to test patients twice and the amount associated with incorrectly switching patients to a second-line ART regimen for the duration of a year.

For both the CD4 and VL monitoring strategies, testing only high risk patients under Scenario A was the most cost-effective of the three scenarios. Under this scenario, however, a high percentage ($>$65%) of patients who have genotypic resistance would be missed regardless of the monitoring strategy. Compared with Scenario A, testing medium and

high risk patients (Scenario B) was more expensive for both the CD4 and VL monitoring strategies, with a lower percentage of missed genotypic resistance cases (20.7% missed for CD4 monitoring, and 25.4% missed for VL monitoring). Of the three scenarios, testing low, medium, and high risk patients (Scenario C) gave the highest sensitivity (98.5% and 94.5% for CD4 and VL monitoring respectively) and lowest specificity (9.4% and 42.1% for CD4 and VL monitoring respectively). Scenario C was also the most expensive of the threshold scenarios for both monitoring strategies.

I extended this analysis by evaluating the dollar cost of each monitoring strategy as a function of the baseline cost to detect 1000 genotypic resistance cases and the cost associated with incorrectly switching patients to a second-line regimen. Under Scenario A, the cost to detect 1000 genotypic resistance cases using CD4 monitoring was halved when compared with VL monitoring. Importantly, the sensitivity for the CD4 monitoring strategy in this scenario was not substantially poorer than its VL counterpart (i.e., 34.5% vs. 42.1%). The cost-effectiveness and diagnostic performance of CD4 monitoring to detect genotypic resistance in *high risk* patients only could be an attractive option for health-care clinics in resource-limited settings.

Unlike Scenario A (testing of high risk patients only), CD4 monitoring was substantially more expensive than VL monitoring in Scenario B (testing high and medium risk patients). While the baseline cost to detect 1000 genotypic resistance cases using CD4 testing was more affordable (than baseline VL testing), this advantage was offset by the higher NNT and number of patients that would be incorrectly switched to second-line regimens. In Scenario B, the percentage of patients incorrectly switched under the CD4 monitoring strategy (27.2%) was substantially higher than that of the VL strategy (5.70%). These results show that CD4 monitoring is not a more cost-effective strategy than VL monitoring when high and medium risk patients are monitored.

Testing of high, medium, and low risk patients (Scenario C) is the most expensive of the three monitoring strategies. The highest number of patients per 1000 genotypic resistance cases would be incorrectly switched to a second-line regimen under Scenario C. The cost of CD4 monitoring is also higher than VL monitoring, for the same reasons outlined in the discussion of Scenario B. Results show that 90.6% would be incorrectly switched to a second-line regimen under Scenario C, thereby substantially increasing treatment costs.

In addition, the VL monitoring strategy had a better sensitivity and specificity. Further evaluation and consultation will need to undertaken to determine if the inclusion of low risk patients in a monitoring strategy can be balanced with the available financial and logistical resources of a given public health-care facility.

A limitation of this study is that all eligible patients with VL >1000 copies/ml not sent for genotypic resistance testing were excluded from the analysis. The results of this analysis show that CD4 monitoring is not always a more cost-effective strategy when compared with VL monitoring. The cost advantage of CD4 testing is offset by its inferior diagnostic performance when used to classify patients that are at a medium and/or low risk of HIV drug resistance.

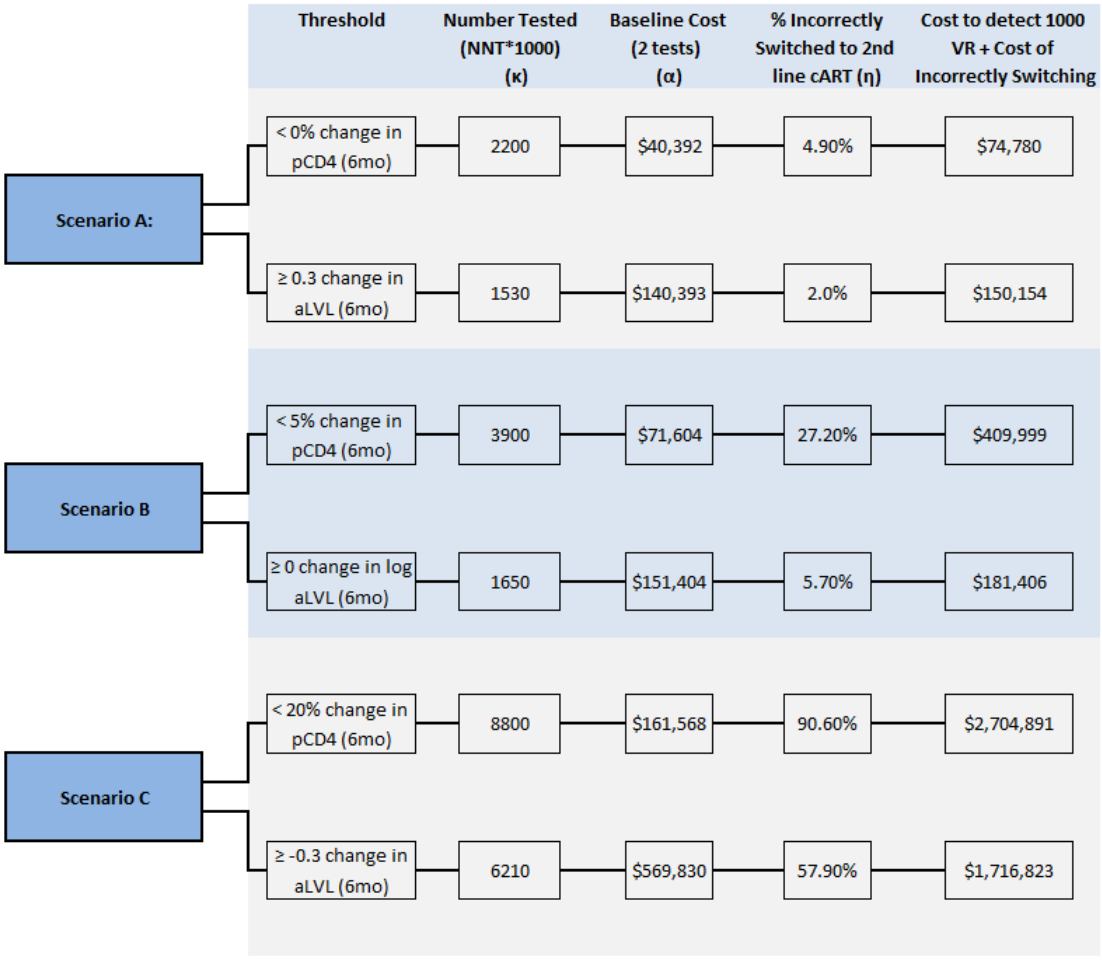

Figure 7.6: Joint cost to detect 1000 genotypic resistance cases and incorrectly switching patients to second-line cART

Chapter 8

Conclusion

I undertook three empirical analyses in this dissertation using data from the Africa Centre for Health and Population Studies. For the first empirical analysis, presented in Chapter 5, I quantified the preventive impact of ART on HIV acquisition risk at the household level. Next, I examined the socio-demographic and structural variables associated with poor adherence to ART in Chapter 6. I continued with the topic of ART adherence in the third empirical analysis, presented in Chapter 7, where I evaluated the diagnostic performance and cost effectiveness of two ART monitoring strategies. I consider each of these analyses to address a real-world topic or problem in the HIV treatment and care domain, and frame these three empirical analyses as the substantive contribution of this dissertation.

Underlying each of these empirical analyses is a conceptual or explanatory framework of health, which I presented in Chapters 2 and 3. In Chapter 2, I addressed the challenging sociological question of how social facts come to be embodied as individual pathology. I suggested that a reasonable starting point would be to consider the complex interaction of various causal factors positioned at different levels in a hierarchical model of health. Such a model would conceptualize a given social fact to operate on lower level factors in the hierarchy in order to affect a particular health outcome. Here, I identified and delineated three such levels, the proximate determinants (Level 1), socioeconomic position (Level 2), and the societal context (Level 3). My aim in this chapter was to motivate a sociological approach to the study of health outcomes based on this proposed model.

I developed the proposed conceptual model in Chapter 3 by discussing the macro-social, micro-social, and individual level factors that are associated with HIV-related outcomes in the sub-Saharan African context. I briefly provided a cursory outline of the viral etiology of HIV, its progression to a global pandemic, and the social determinants that make the epidemic particular to the African continent. I argue in this chapter that the complex

epidemiology of HIV/AIDS in this context warrants the use of a conceptual framework that addresses the broad range of social, behavioral, and biological factors known to be associated with the spread and treatment of HIV.

In Chapter 3 I reviewed the proximate determinants of HIV: these are the behavioral and biological mechanisms through which macro- and micro-social factors are conceptualized to affect HIV-related outcomes. Much of the work in this chapter was devoted to the household context—the micro-social level of the proposed model. The household was conceptualized to be the site where community level effects were mediated, and where social relationships defined, constrained, and reproduced a range of HIV-related behaviors. In Section 3.1.3 I briefly discussed four macro-social factors of the proposed conceptual model, which were the 1) social attitudes and beliefs, 2) institutions and structures, 3) epidemiological conditions, and 4) demographic characteristics of an individual's community.

The proposed multilevel model of health was used for each of the three empirical chapters to explain how the various HIV-related outcomes are affected by the proximate, behavioral, or social variables. Take for example the first empirical analysis where I investigated if ART usage in the household was associated with a reduction in HIV acquisition risk. Under the assumption of heterosexual HIV acquisition risk, I considered the household to be a proxy for the potential sexual partners of the repeat-tester. Here, the hazard of HIV acquisition would be a function of the three biological determinants: the rate of sexual contact with co-residents in the household, the probability of acquiring HIV in one sexual contact with an infected co-resident, and the duration of susceptible time in the household. Each biological determinant would in turn be affected by one or more of the HIV proximate determinants (shown in Figures 3.2 and 3.3). To illustrate, the duration of susceptible time would be reduced if a repeat-tester migrated to a household with no infected co-residents. ART usage among co-infected residents would reduce the probability of acquisition in one sexual act—since the transmission of HIV between serodiscordant sexual partners is strongly correlated with the concentration of the virus in the blood—which treatment is designed to reduce. A repeat-tester's rate of contact with infected co-residents would be substantially reduced in he or she was in a monogamous relationship and practicing safe sex. The decision to practice safe sex would ultimately be shaped or reinforced by the prevailing social and patriarchal norms toward abstinence, condom use, monogamy, concurrency, and gender equality.

The proposed multilevel conceptual framework can be applied to the second empirical analysis where I selected virologic failure as a proxy for imperfect adherence to ART. As cited in Section 6.1, high adherence to ART is the strongest predictor of virologic suppression. Therefore, any socio-demographic or structural factor must operate through this (behavioral) proximate determinant—ART usage—in order to vary the amount of HIV in a patient's blood. Under the multilevel conceptual model, societal level factors associated with migration, residential mobility, distance to the clinic, and transport costs are conceptualized to facilitate, interrupt, or modify a patient's adherence to treatment. For example, frequent migration would break a patient's regular contact with his or her treatment clinic. Additional resources, time, and cost would then be required to locate a new treatment clinic at the point of destination. Under this illustrative scenario, these macro- and micro-social challenges would result in treatment interruptions that reduce the level of ART in the patient's system, allowing HIV to replicate more efficiently and leading to mutant strains that are resistant to the current treatment regimen.

It is for this reason that adherence monitoring is the central aim of Chapter 7. Here, public health efforts to monitor treatment response to ART would help to detect adherence issues early, resulting in the introduction of additional treatment support services or alternative treatment options. These public health initiatives would ensure that the patient maintains an adequate level of ART in the system to sufficiently suppress the amount of HIV. Under conditions of high patient interaction with the treatment clinic, monitoring strategies would facilitate efforts to assess patient response to ART. However, as discussed in Chapter 7, the economic realities of resource-limited settings often limit the implementation and distribution of standard or recommended treatment monitoring strategies. In this respect, economic and institutional constraints, which are societal level factors that affect the efficacy and implementation of monitoring strategies, are conceived to operate through a specific proximate determinant—ART usage and adherence—to affect the development of HIV drug resistance.

Given this brief discussion, I therefore argue that the proposed multilevel model is continually operating in the background of the empirical analyses even though it is not explicitly discussed or referenced in these chapters. The multilevel model provides a general causal framework by which the societal, socio-economic, and behavioral factors of interest

come to affect the specified HIV-related outcome, whether this be acquisition, virologic failure, or genotypic resistance. It is to this degree that the theoretical and empirical work of this dissertation is synthesized. As mentioned, the acknowledged primacy of the empirical chapters can be justified by the grave and pressing issues that confront HIV prevention and management efforts in sub-Saharan Africa. It is my hope that the work presented in this dissertation can contribute to a branch of sociology that is concerned with the evaluation of program interventions; that is invested in the production of solutions to the material, technical, and immediate problems of the real-world domain; and that is interdisciplinary in its scope and application.

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Appendix

Material for Chapter 6

Individual Fixed Effects Model: Let Y_{ij} be a random variable denoting the CD4 count response at time-point i for patient j. Let x_{ij} be the difference in months between the CD4 test date at time-point i and the baseline CD4 count test date (time-point $i = 1$) for patient j. Let m indicate the total number of patients, and n the total number of time-points in the sample. An individual fixed effects model acknowledges the grouping structure of the data for which the jth patient has $i = 1, \ldots, n_j$ time-points, where $n_j > 1$ and the total number of time-points for the sample is $\sum_{j=1}^{m} n_j = n$. The observations $(x_{ij}, y_{ij}), \ldots, (x_{n_j m}, y_{n_j m})$ are realizations of the paired sequence $(x_{ij}, Y_{ij}), \ldots, (x_{n_j m}, Y_{n_j m})$ for the $j = 1, \ldots, m$ patients and $i = 1, \ldots, n_j$ time-points.

The individual fixed effects model in matrix notation is given by:

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\epsilon} \tag{8.1}$$

where $\mathbf{Y}$ is a $n \times 1$ response vector, $\mathbf{X}$ is a $n \times 2$ matrix with the first column set to ones and the second column set to the values of the predictor variable x, $\boldsymbol{\beta}$ is a 2×1 vector of coefficients, and $\boldsymbol{\epsilon}$ is a $n \times 1$ vector of statistical errors.

Three important assumptions are made about the error terms: 1) They are normally distributed random variables, with 2) expectation equal to zero and common variance σ^2; and 3) are independent (that is, the value of one error does not provide information about the value of another error).

The individual fixed effects model is:

$$y_{ij} = \beta_{0j} + \beta_{1j} x_{ij} + \epsilon_{ij}, \quad i = 1, \ldots, n_j;\ j = 1, \ldots, m \tag{8.2}$$

where β_{0j} and β_{1j} are the patient-specific intercepts and slope respectively, x_{ij} are the number of months between the CD4 test date (time-point i) and the baseline CD4 count test date (time-point $i = 1$) for patient j, and ϵ_{ij} is the ith statistical error for patient j. An individual fixed effects model used the ordinary-least squares (OLS) method to obtain

the $\hat{\boldsymbol{\beta}}$ estimators of $\boldsymbol{\beta}$, which consists of minimizing the residual sum of squares (rss) for the jth patient:

$$\text{rss}_j = \sum_{i=1}^{n_j} (y_{ij} - \hat{y}_{ij})^2 \tag{8.3}$$

where y_{ij} is the observed response and $\hat{y}_{ij} = \hat{\beta}_{0j} + \hat{\beta}_{1j} x_{ij}$ is the fitted value for patient j at time-point i. The residual sum of squares for the full sample is minimized by minimizing the residual sum of squares for each patient in the sample (Fox, 2008).[1]

[1] My decision not to use a random effects model to obtain the patient-specific CD4 count slopes is explained in greater detail in Vandormael (2014).

	Submodel 1		
	OR	**(CI)**	**p-value**
Male	1.269	(1.019–1.581)	0.034
Age	0.970	(0.959–0.982)	0.000
Highest education:			
No school	(Ref.)		
Primary school	1.237	(0.738–2.074)	0.419
High school	1.310	(0.790–2.173)	0.295
Tertiary education	1.257	(0.744–2.124)	0.393
Employed >50% time	0.961	(0.777–1.188)	0.711
External migration (more than once)	1.312	(1.038–1.659)	0.023
Disability grant received	1.798	(0.384–8.425)	0.457
Constant	0.347	(0.171–0.705)	0.003
N	3525		

Table 8.1: Submodel 1: Logistic regression output for the socio-demographic factors

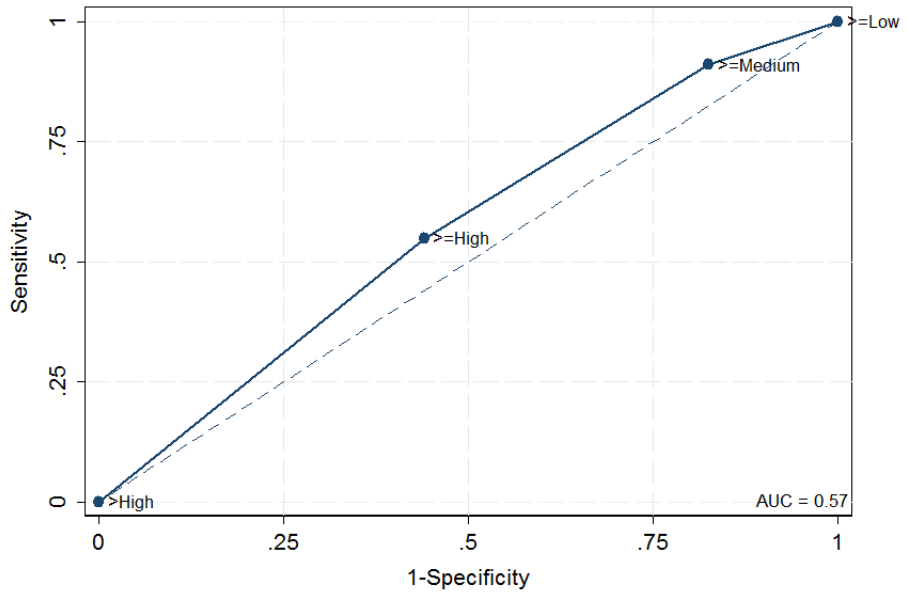

Figure 8.1: ROC graph for submodel 1 (socio-demographic predictors)

	Submodel 2		
	OR	**(CI)**	**p-value**
Km (line) to nearest clinic	1.003	(0.943–1.065)	0.935
1.PreviousARTYes	1.299	(0.917–1.839)	0.140
Yes	1.565	(1.008–2.430)	0.046
Duration of ART (months)	1.125	(1.110–1.141)	0.000
Ave. months between clinic visit	0.801	(0.771–0.831)	0.000
Clinic visit count	0.239	(0.205–0.278)	0.000
Changed clinic	2.279	(1.754–2.961)	0.000
Constant	2.492	(1.604–3.872)	0.000
N	3525		

Exponentiated coefficients

Table 8.2: Submodel 1: Logistic regression output for the socio-demographic factors

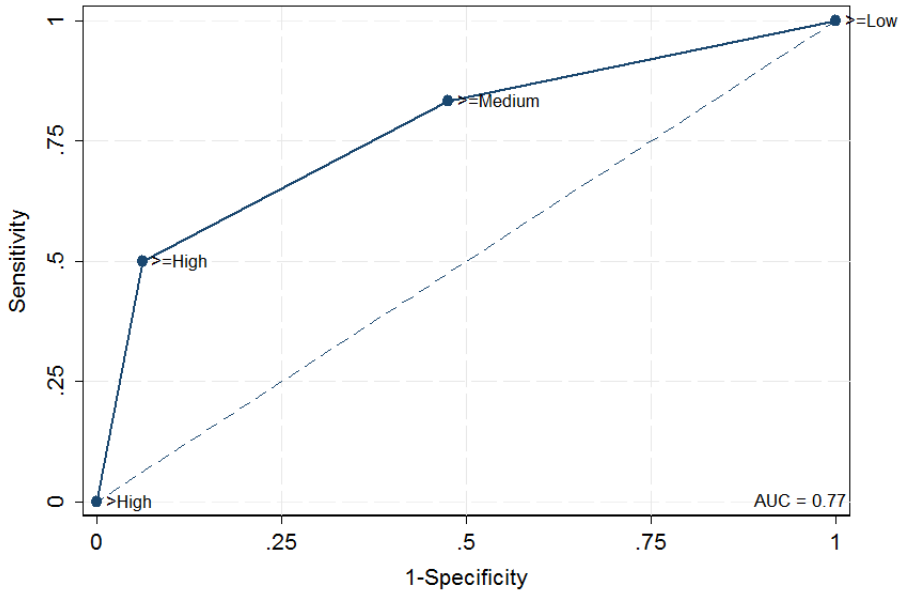

Figure 8.2: ROC graph for submodel 2 (structural predictors)

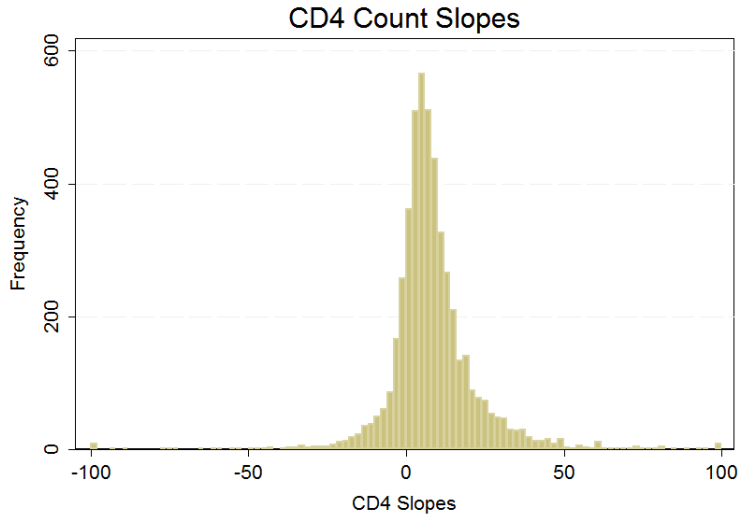

Figure 8.3: Distribution of CD4 count slopes obtained from the individual fixed effects model.

CD4 count slopes	Freq.	Perc.
$<$ -10	99	2.8%
-10 to -1	411	11.7%
0 to 5	1,114	31.6%
$>$ 5	1,901	53.9%
Total	3,525	100.0%

Table 8.3: CD4 count slopes by category

		Submodel 3	
	OR	**(CI)**	**p-value**
CD4 Count Slope:			
>5	(Ref.)		
<−10	43.060	(26.338–70.399)	0.000
−10 to <0	14.536	(11.045–19.130)	0.000
0 to 5	2.008	(1.536–2.626)	0.000
Age:			
16–19	(Ref.)		
20–24	0.360	(0.163–0.792)	0.011
25–29	0.505	(0.245–1.041)	0.064
30–34	0.460	(0.223–0.946)	0.035
35–39	0.333	(0.160–0.693)	0.003
≥ 40	0.188	(0.091–0.388)	0.000
Male	1.257	(0.983–1.607)	0.068
Constant	0.175	(0.087–0.352)	0.000
N	3525		

Table 8.4: Submodel 3: Regression output for the CD4 count, age, and sex predictors

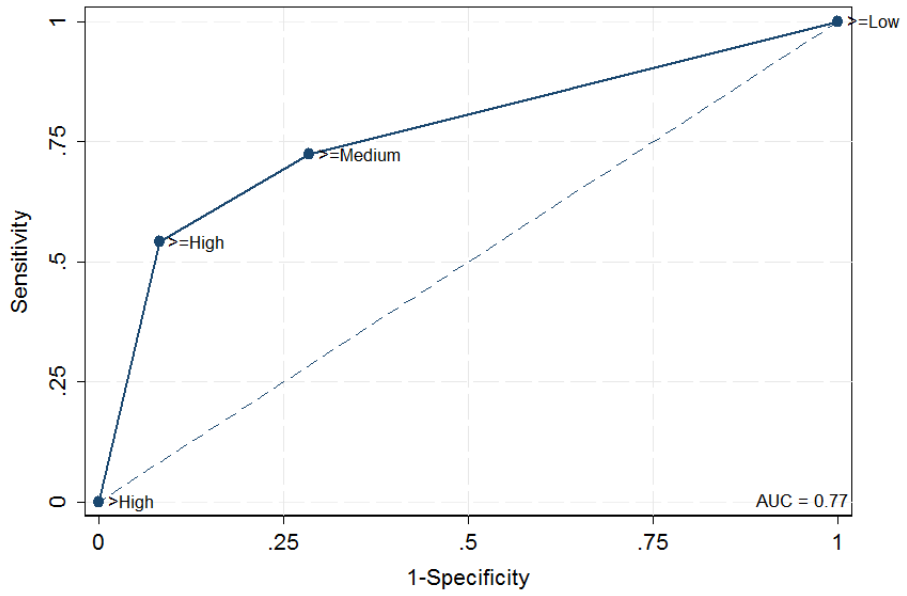

Figure 8.4: ROC graph for submodel 3 (CD4 count predictor)

		Submodel 4	
	OR	**(CI)**	**p-value**
CD4 Count Slope	0.892	(0.879–0.905)	0.000
Age	0.961	(0.949–0.974)	0.000
Male	1.124	(0.859–1.471)	0.393
Prop. time employed	0.886	(0.659–1.190)	0.421
External migration	1.305	(0.582–2.923)	0.518
Changed clinic	1.797	(1.349–2.394)	0.000
Clinic visit count	0.249	(0.211–0.295)	0.000
Duration on treatment (mths)	1.106	(1.089–1.122)	0.000
Duration between clinic visits (mths)	0.802	(0.771–0.835)	0.000
N	3525		

Table 8.5: Submodel 4: Regression output for the CD4 count, age, and sex predictors

```
** Code to maximize the AUC
** First compute predicted probabilities for the submodel
predict phat1 if e(sample)
** Set the variables to be populated for each iteration
gen Lower = .
gen Upper = .
gen AUC= .
local irow = 0
** Now iterate using incremental values of 0.05
forvalue ub = 0(0.05)1 {
        forvalue lb = 0(0.05)0.5 {
                local ++irow
                capture drop profile
                gen profile = 2     if phat1 >‘ub’
                replace profile = 1 if phat1 >=‘lb’ &  phat1 <=‘ub’
                replace profile = 0 if phat1 < ‘lb’
                replace Lower = ‘lb’ if _n==‘irow’
                replace Upper = ‘ub’ if _n==‘irow’
                qui roctab Failure profile
                replace AUC = ‘r(area)’ if _n==‘irow’
                }
}
```

Material for Chapter 7

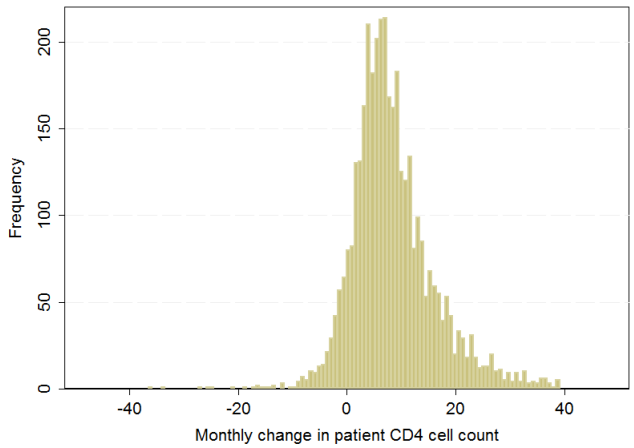

Figure 8.5: Change in patient CD4 cell count per month

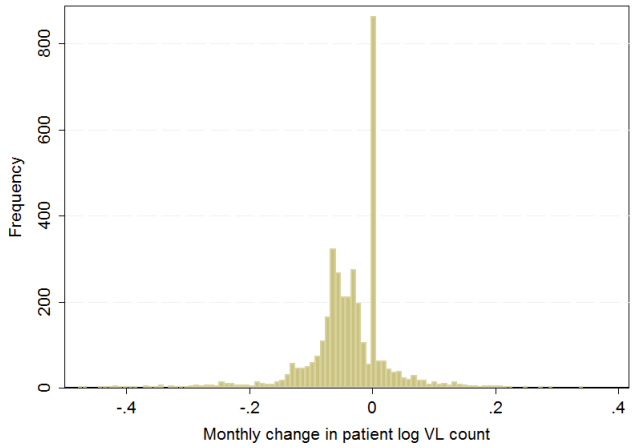

Figure 8.6: Change in patient VL count per month