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Approval Sheet

Psychosocial Associations with Virological Failure among Patients on Antiretroviral Therapy at McCord Hospital in KwaZulu-Natal, South Africa

By

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Master of Public Health

Global Epidemiology

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Abstract Cover Page

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By

Rachel Kearns

B.A., Emory University, 2007

Thesis Committee Chair: Patrick Sullivan, DVM, PhD

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An abstract of

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Abstract

Psychosocial Associations with Virological Failure among Patients
on Antiretroviral Therapy at McCord Hospital in KwaZulu-Natal, South Africa

By Rachel Kearns

Objective
Understanding factors associated with virological failure may improve prevention, diagnosis and treatment of virological failure among patients on ART.

Design
The RFVF is a study of cases with virological failure (VL > 1,000 copies/ML) and controls with virological suppression (VL ≤ 1,000 copies/ML) after at least 5 months on their first ART regimen at McCord Hospital in Durban, South Africa between October 2010 and June 2012.

Methods
Patients completed a questionnaire on medical history, psychosocial factors, depression using Kessler-10, and socioeconomic status, retrospective chart reviews were completed, and drug resistance genotyping was performed on cases. Using multivariate logistic regression, this sub-study assessed the significance of psychosocial factors on virological failure among the full study population, men and women separately.

Results
158 cases and 300 controls were enrolled in the study. The sample was predominantly female (64.6%), black Zulu (92%), and Christian (85.8%). In multivariate analysis for the full sample, male gender (OR=2.42, 95% CI 1.51-3.88), younger age (OR=0.83, 95% CI 0.72-0.94), shorter duration of treatment (OR=3.83, 95% CI 2.06-7.13 shortest vs. longest quartile) reporting any depressive symptoms (OR=2.21, 95% CI 1.35-3.61), being not active or having no faith compared to being somewhat or very active in faith (OR=1.60, 95% CI 1.02-2.50), having unsafe sex in prior 6 months (OR=2.50, 95% CI 1.17-5.32), having one or more HIV positive partner or family member (OR=1.70, 95% CI 1.03-2.82), having a treatment supporter (OR=2.02, 95% CI 1.13-3.64), and disclosing HIV status to friends (OR=2.02, 95% CI 1.23-3.33) were associated with virological failure. Among men, having at least one family member who died of HIV (OR=2.98, 95% CI 1.29-6.91) was also significantly associated with virological failure.

Conclusions
Several psychosocial factors are associated with virological failure in this setting. Patients experiencing failure were more likely to have a treatment supporter and family members with HIV, depressive symptoms, have no active faith, have unsafe sex and disclose their status to friends. Future studies should employ a longitudinal design to assess causality and ideally improve screening and identification of virological failure.

Cover Page

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Table of Contents

Chapter I: Background/Literature Review

Introduction

South Africa has more people living with HIV/AIDS than any other country in the world (1). According to UNAIDS, in 2009, an estimated 5.6 million people in South Africa were living with HIV/AIDS, of which 5.3 million were adults over the age of 15 (1). Women are estimated to make up the majority of people living with HIV/AIDS, accounting for 3.3 million, or 62% of prevalent cases (1).

UNAIDS estimates a HIV prevalence rate of 17.8% in the whole South African population in 2009, up from 17.1% in 2001 (1). Although the prevalence rate is up from 2001, the incidence rate of new HIV infections has declined; in adults the incidence rate in 2009 was 1.49% compared to 2.35% in 2001 (1). The South Africa country progress report describes a plateau in the national HIV prevalence using antenatal HIV sero-prevalence data (2). Despite a reduction in the number of new HIV infections annually, overall prevalence of HIV is not declining since antiretroviral therapy (ART) allows people with HIV to live longer. The South Africa progress report estimates a 29.3% prevalence of HIV among pregnant women aged 15-49 in antenatal clinics in 2008, which is stable over the prior three years (2). The province of KwaZulu-Natal (KZN) is particularly hard-hit by the HIV epidemic. Antenatal HIV prevalence is estimated at 38.7% compared to the national average of 29.3% (2).

South Africa has the largest public-sector ART program in the world (3). Beginning in 2003, ART became available through the South African government free of charge (4). However, rollout of ART did not reach many provinces until 2004, and then increasingly so in 2005 with the introduction of President's Emergency Plan for AIDS Relief (PEPFAR) funding (5). Prior to government rollout, ART had limited availability in South Africa in private sectors and through research studies. By November 2009, an estimated 56% of adults and children in need of ART were in treatment through the public sector (2). However, based on the WHO 2010 guidelines (which recommend initiating ART for people living with HIV with a CD4 count of 350 cells/mm^3

or lower, or WHO clinical stage 3 or 4 when CD4 testing is unavailable), only an estimated 37% of people needing treatment were receiving ART in South Africa (1, 6).

According to the 2011 South Africa census, KwaZulu-Natal province has the second highest population in South Africa, with almost 20% of South Africans (7). 86.8% of the population in KZN is black, 1.4% is Coloured, 7.4% Indian/Asian, and 4.2% white (7). The province is predominantly Zulu, with 77.8% of the population speaking IsiZulu as their first language (7)..

Background on McCord Hospital

McCord Hospital is a state-funded hospital located in Durban, South Africa, the largest city in the KwaZulu-Natal province. Sinikithemba Clinic is the outpatient HIV/AIDS clinic of McCord Hospital. Sinikithemba was established in 1998 to provide care for HIV-positive patients and their families. In 2004, after receiving funding from PEPFAR, Sinikithemba's ART program was expanded (8). Currently, the clinic is subsidized by PEPFAR and the KwaZulu-Natal Department of Health, and it is a regional referral center for ART (9, 10). The Sinikithemba clinic serves 3,000 to 4,000 adults per month, of which approximately 70% are black, Zulu speakers, 20% are Indian and 10% are white (9). The cost to attend the clinic is US $25 per visit (9). HIV care follows the guidelines outlined by the South African Department of Health, with HIV-1 viral load (VL) and CD4 cell count monitoring every 6 months (11). Adherence training and counseling is provided by the clinic prior to initiating ART and any time the patient has an elevated viral load measure (11). Patients who doctors identify as having psychological issues or family challenges are referred to the Psychology Clinic, where they receive assessment and therapy at no additional cost. The Psychology Clinic will send a note back to the provider at Sinikithemba, and will recommend anti-depressants or request subsequent visits as necessary (Sally John, personal communication).

HIV Treatment in South Africa

The South African Department of Health eligibility criteria for starting ART include one or more of the following:

1. CD4 count less than or equal to 350 cells/mm3 irrespective of clinical stage
2. Irrespective of CD4 count, all types of TB and/or WHO stage 3 or 4 condition (12).

According to the South African Clinician Society Guidelines for ART, indications for initiating ART are based on clinical diagnoses, CD4 counts, pregnancy and/or partner HIV status. Clinical diagnoses that are indications for ART include WHO clinical stage 3 and 4 conditions (most commonly tuberculosis), other severe HIV-related disorders (immune thrombocytopenia, thrombotic thrombocytopenic purpura, polymyositis, lymphocytic interstitial pneumonitis), non HIV-related disorders (malignancies, hepatitis B, hepatitis C), and any condition that requires long-term immunosuppressive therapy. ART is recommended when CD4 counts are below 350 cells/µl, and when the patient is the HIV-infected partner in a serodiscordant relationship, regardless of CD4 count or clinical diagnoses (13).

According to the South African Department of Health, first-line treatment for new patients includes tenofovir (TDF) + lamivudine (3TC) or emtricitabine (FTC) + efavirenz (EFV) or nevirapine (NVP). If the patient has a contraindication to TDF (i.e. renal disease), zidovudine (AZT) + 3TC + EFV or NVP is prescribed (12, 14). Current treatment guidelines from the South African Clinicians Society recommend that first-line regiments include a non-nucleoside reserve transcriptase inhibitor (NNRTI) and two nucleoside analog reverse-transcriptase inhibitors (NRTIs). The preferred NNRTI is EFV, but NVP can also be used. In addition to the NNRTI, the guidelines recommend a two-drug NRTI combination of either 3TC OR FTC plus TDF, AZT or abacavir (ABC) (13).

Standard national ART regiments for second-line therapy are based on the first-line ARVs used. If the patient failed on a stavudine (d4T) or AZT-based first-line regimen, they

recommend TDF + 3TC or FTC + lopinavir/ritonavir (LPV/r). If patient failed in a TDF-based first-line regimen, use AZT + 3TC + LPV/r (14).

Despite the increase in ART availability, continued success of ART depends on effective monitoring and treatment of HIV patients with virological failure. Rapid scale-up of ART availability in sub-Saharan Africa presents new challenges in HIV care, including identifying and managing virological failure to maintain lifelong ART therapy for HIV patients. When patients with virological failure are not identified and managed accordingly, this can have a serious impact on treatment outcomes. If patients continue on a failing regimen, it could compromise their immunological and clinical state, as well as lead to replication of viruses with resistance to one or more antiretroviral drugs (15).

Virological failure is often but not always associated with drug resistance. Distinguishing between patients with drug resistance and those without can improve targeted treatment regimens and counseling. Second-line therapies are typically more expensive and less accessible, so it is ideal to switch to these regimens only when necessary. Correctly identifying VF and drug resistance can improve diagnosis and outcomes in several ways. One, switching treatment for patients with immunologic failure but not VF (typically if no viral load testing is available to diagnose VF) unnecessarily raises treatment costs and toxicity for the patients (15). Second, if a patient has VF but not immunologic failure, but virologic testing is not available to identify VF, then the patient could accumulate more resistant mutations and thus limit future ARV treatment options, particularly in resource-poor settings that may have a limited variety of available ARVs (15). Third, for patients who experience VF, but do not have drug resistance, it is ideal to improve their adherence to the current regimen and avoid second-line therapies and the increased cost and toxicity from those treatments.

Defining Treatment Failure and Virological Failure

The World Health Organization (WHO) recommends criteria for indicating treatment failure in patients on ART, but cites virological failure as the most sensitive indicator of treatment failure in patients on ART.(6) According to WHO's 2010 recommendations, criteria for treatment failure are as follows:

1. Clinical Failure: New or recurrent WHO stage 4 condition (and certain WHO clinical stage 3 conditions like pulmonary TB or severe bacterial infections)
2. Immunological Failure: Fall of CD4 count to baseline (or below) OR 50% fall from on-treatment peak value OR persistent CD4 levels below 100 cells/mm^3
3. Virological Failure: Plasma viral load above 5,000 copies/mL (6).

Clinical symptoms can be misleading, since some symptoms of drug toxicity are comparable to VF, or they can occur even when ART is successful (for example, extrapulmonary tuberculosis and Kaposi's sarcoma) (16). In addition, immune reconstitution inflammatory syndrome (IRIS), which exacerbates or unmasks symptoms of opportunistic infections, can occur when patients initiate ART, further confusing diagnosis of treatment failure using clinical symptoms (17, 18). Thus, VF is the most useful indicator of treatment failure in patients on ART. Though WHO defines the threshold for VF at 5,000 copies/mL, WHO notes that the optimal viral load cutoff has not yet been determined (6). They recommend implementing an adherence intervention after an initial viral load greater than 5,000 copies/mL; if a repeat viral load measurement is also above 5,000 copies/mL, the patient should switch the second-line therapy (6).

Despite being outlined by the WHO, criticisms and questions remain about the accuracy of these criteria. In high-resource settings, guidelines recommend using a cutoff of 50 copies/mL to indicate VF, since drug resistance mutations can occur at these lower levels of HIV RNA (19). Many studies to assess virological failure based on viral load suffer limitations, because they cannot differentiate between true VF and viral "blips" from viremia when ART is successful (18). To create the most cost efficient strategy which optimizes treatment outcomes, it will be

necessary to define the best HIV RNA concentration cutoff, “at which immunological and clinical deterioration happen, and accumulation of important resistance mutations can be expected” (16).

South Africa has standardized criteria for diagnosing virological failure. The South African Clinicians Society defines treatment failure using virological criteria; failure is a confirmed HIV viral load of >1,000 copies/mL in two measurements taken one to three months apart (13). The South African Department of Health guidelines mirror this criteria, with treatment switches only recommended when virological failure occurs, defined as a HIV viral load greater than 1,000 copies/mL (14).

Past studies at McCord Hospital have used the South Africa guidelines for HIV RNA viral load cutoffs to define virological failure. In their cohort study of outcomes after ART failure at McCord Hospital, Murphy et al. defined VF as having a single viral load of ≥1,000 copies/mL during their initial combination of ART (11). Marconi et al. defined virological failure the same when assessing the prevalence of drug resistance among patients who fail their first ART (10). A systematic review by Barth et. al of virological outcomes also considered VF when HIV-1 RNA was greater than 1,000 copies/mL.(15) However, some studies in South Africa and other countries in sub-Saharan Africa have used a threshold of 400 copies/mL to define VF (16, 20).

A study by Fox et al. assessed different viral load thresholds and their implications on virological failure and treatment switches among 25 national treatment programs in South Africa (21). In one analysis, they defined treatment failure as patients on their first-line therapy for at least six months with one viral load above 400 copies/mL and then a consecutive viral load measure at different thresholds – greater than or equal to 400, 1,000, 5,000, or 10,000 copies/mL on their first therapy (21). In another analysis, Fox et al. used a viral load cutoff of 1,000 copies/mL, since that was the minimum viral load measurement that the clinics used to switch to second-line treatments (21). Using these thresholds, Fox et al. found that between 8% and 17% of patients failed first-line treatment by 5 years. Prevalence of failure was similar when using a threshold of 400 and 1,000 copies/mL, but dropped substantially when using a 5,000 or 10,000

cutoff (21). Thus, the difference between the WHO guidelines and South Africa guidelines for treatment failure can mean a substantial change in the number of patients diagnosed with treatment failure.

Prevalence of Virological Failure

Virological failure is estimated to affect 4.9% to 19% of patients on first-line ART using varying viral load thresholds (15, 19, 22-24). One systematic review of virological outcomes in sub-Saharan Africa found that using a viral load threshold of 1,000 copies/mL, 15% of patients experienced VF (15). Virological success, defined as a viral load with fewer than 500 copies/mL, was reported in 78% of patients after six months on therapy, with prevalence in studies from South Africa ranging from 61% to 92% virological success (15). A systematic review of ART clinical trials found virological failure at 48 weeks after initiation in 4.9% of patients receiving two NRTIs and an NNRTI and 5.3% of patients treated with an 2 NRTIs and a boosted protease inhibitor (with VF defined as a viral load of >400 copies/mL after achieving <400, or failure to achieve <400 copies/mL after 24 weeks on therapy) (22). A study in rural Limpopo in South Africa found that 16% of patients on ART for at least three months failed first-line therapy, defined as an HIV RNA >1,000 copies/mL (23). Using a VF definition of repeated viral loads greater than 50 copies/mL, El-Khatib et al. found a 19% prevalence in Soweto, South Africa (19). In Khayelitsha near Cape Town, South Africa, 14% of patients on ART experienced virological failure after 5 years on treatment (defined as two consecutive viral loads greater than or equal to 5,000 copies/mL) (24). Though not measuring virological failure directly, a study by Mutzevedzi et al. in KwaZulu-Natal found that 23% of patients had a detectable viral load (≥25 copies/mL) 12 months after initiating ART (3).

Even though only a small percentage of ART users experience VF, because of the size of the HIV epidemic in South Africa, VF affects a large number of people. As more patients in South Africa gain access to ART each year, more newly infected individuals initiate treatment,

and patients stay on treatment for longer periods of time, virological failure will become a growing problem.

Diagnosing and Managing Virological Failure

To improve treatment outcomes and care among HIV-positive patients, it is important to identify virological failure and, if necessary, switch patients to second-line regimens that may be more effective. However, it is difficult to diagnose and manage virological failure in resource-limited settings in sub-Saharan Africa (18). Many resource-poor settings lack the laboratory resources and technology required to accurately diagnose and manage VF, including CD4-lymphocyte count, plasma HIV RNA concentration, and drug-resistance profiles (18). These laboratory procedures can measure viral loads necessary to diagnosis VF, and identify major resistance to ARTs that can inform whether to switch therapies and if so, which ARVs to prescribe. Routine viral monitoring is the gold standard for identifying VF (21).

Without virological monitoring, physicians and HIV patients have to rely on clinical and immunological monitoring to identify treatment failure and switches to second-line treatment. However, physicians considers these methods suboptimal to viral monitoring because they do not allow for a timely identification of VF, and thus prevention of viral load replication, potential resistance mutations, and protection of drug susceptibility in subsequent ART regimens (6). To improve cost efficiencies in viral load testing, it may be useful to perform targeted VL testing on patients that show other signs (clinical or immunological) of failing treatment (6).

Multiple studies show the poor predictive ability of non-virological measures to predict VF. Fox et al. cite the poor predictive ability for clinical and immunological indicators of VF, and thus the importance of improving access to viral load testing (21). In a study of HIV treatment outcomes in rural South Africa, relying on immunological indicators alone, VF would have been missed in 56% of patients, and 46% of patients would have been misclassified as experiencing VF (23). Another study found that almost two-thirds of patients with immunological failure based

on CD4 cell count were virologically suppressed, thus using immunological criteria to assess treatment outcomes is ineffective (19). In a study of ten treatment programs in Africa and South America, Keiser et al. assessed the accuracy of WHO immunological indicators to predict VF (CD4 counts persistently less than 100 cells/μl, a fall below baseline CD4 count, or a fall of >50% from peak value) at a cutoff of 500 copies/mL. They found that immunological criteria had a sensitivity of 12.6%, specificity of 97.3%, positive predictive value of 19.0%, and negative predictive value of 95.7% (25). The high specificity (correctly identifying non-cases), and the high negative predictive value (negative tests indicates non-case) show the ability to rule out VF using the immunological criteria, but the low sensitivity measure reinforces the poor diagnosing ability of these criteria (6, 25).

Unique among countries with high HIV burdens, South African ART programs implement routine viral load testing (21). The South African National Department of Health recommends that patients on ART have viral load testing 6 months after ART initiation, 12 months after, and every subsequent 12 months (12). If the viral load is >1,000 copies/mL, they recommend to check the patient's adherence, compliance and tolerability, possible drug interactions and assess psychological issues. Then, repeat the viral load test two months later and switch to second-line therapy if second viral load is still >1,000 copies/mL (12). Despite South Africa's viral load standards, finding risk factors or methods to identify VF without viral load testing in South Africa could improve treatment outcomes in other settings without access to these tests.

Selecting appropriate ARVs for second-line therapies requires training and expertise that may be lacking in some resource-poor settings.(6) In addition, appropriate second-line regimens may not be available in rural and peripheral clinics in low-resource countries (18). Harries et al. cites the case of Malawi, where recommended second-line therapies are not always available because of the high cost and because there are not enough providers with the expertise to prescribe them (18). Without providers who have expertise in the complicated second-line

therapies, patients may not receive adequate adherence guidance which could result in poor adherence to these treatments (18).

Harries et al. identify strategies to improve diagnosis and management of ART failure. They describe the need for a composite diagnostic tool for ART failure that includes treatment and adherence history, clinical events and laboratory results. However creating such a tool that is simple enough to be used in busy, low-resource settings will be difficult (18). Creating a point-of-care (POC) viral-load test will improve diagnosis of VF (18). Harries et al. define the necessary parameters for such a test to be useful in rural areas of sub-Saharan Africa: "simple to use and easy to read; independent of instrumentation or electronics; robust and able to withstand increased ambient temperatures without cold-chain shipment or storage; long shelf-life (longer than 12 months); and inexpensive (no more than $2 per test to manufacture)" (18). It will also be necessary to define the optimum threshold of HIV RNA concentrations to indicate VF. VL tests can also indicate the need for additional adherence counseling or patient support, and potentially prevent switching to expensive second-line therapies if these areas are improved first (18). Estill et al. used mathematical modeling to assess the cost-effectiveness of point-of-care viral load monitoring, and found that it was cost-effective when considering that identifying high viral loads reduces the number of new HIV infections and leads to more targeted adherence counseling (26).

Causes of Virological Failure

A diagnosis of virological failure can occur in patients with and without drug resistance mutations. The South African Clinicians Society cite the major causes of virological failure to be inadequate patient adherence, prior use of single-dose NVP for PMTCT, drug interactions that decrease ART concentrations, and transmitted drug resistance (13).

Approximately 70% – 87% of patients failing first-line therapy had at least one major drug resistance mutation (10, 11, 22). In Murphy et al.'s cohort study of outcomes after first ART failure, 87% of patients had at least one major resistance mutation, while the remaining 13% had

the wild-type genotype (11). In Marconi et al.'s study of patients who failed their first highly active antiretroviral therapy (HAART) regimen in KwaZulu Natal, South Africa, 83.5% of patients had at least one drug resistance mutation, 64.3% had resistance mutations to at least one drug in two classes, and 2.6% had resistance mutations to at least one drug in three classes (10). A systematic review of ART clinical trials found no detectable resistance in approximately 30% of patients with VF (22). As ART use increases in South Africa, so will the prevalence of drug-resistance mutations. In sub-Saharan Africa, prevalence of any drug-resistance mutation increased by approximately 14% annually since rollout of ART, and NNRTI resistance increased by 23% per year (27).

The development of drug resistance can depend on the types of ARVs used in first-line therapy. In a review by Barth et al., all patients who experienced VF had been treated with NRTIs at the time of failure, 82% had also been treated with NNRTIs, and 16% with protease inhibitors (PIs) (15). Marconi et al. found that the most common mutations were associated with NNRTI and NRTI drug classes (10).

Exposure to ARVs prior to ART initiation through prevention of mother-to-child transmission (PMTCT) or prophylaxis can also lead to VF. Women who use a single-dose nevirapine (sdNVP) in PMTCT can select drug resistance when using ART after pregnancy (16). El-Khatib et al. found a two-fold increase in the odds of VF among patients with any exposure to ARVs before ART initiation, when controlling for age and sex (19).

Inadequate medication adherence is a major risk factor for virological failure and poor treatment outcomes. In one study, patients with no major resistance mutations suffered from higher mortality and loss-to-follow-up than patients with drug resistance, which could possibly indicate poor medication adherence in these individuals regardless of ARV type (11). There is not a direct relationship between poor adherence and virological failure, and the level of adherence necessary to maintain viral suppression may decrease with more time successfully suppressed on ART (28, 29). Current first-line medications based on NNRTIs and boosted PIs require only a

moderate level of medication adherence (approximately 70-90%) to experience virologic suppression (16). In Rosenblum et al.'s cohort study in San Francisco, a lower risk of virological failure was associated with being on a NNRTI-based ART regimen (29). In the same study, the probability of virological failure after 12 months of continuous viral suppression was significantly lower than the probability of VF after 1 month suppressed for all subjects with at least a 50% adherence level (29). While suboptimal adherence may not lead to VF in all people on ART, it is ideal to promote 100% adherence for best possible treatment outcomes.

Many past studies show a significant impact of poor adherence on virological and treatment failure while on ART. In a study of ART adherence in a Cape Town, South Africa township, suboptimal adherence was significantly associated with VF when controlling for age and baseline CD4 count (30). El-Khatib et al. found a significant association between incomplete adherence and virologic failure in Soweto, South Africa after adjusting for age and sex, with the odds of VF almost tripled among those with poor adherence (19). In a study of treatment outcomes in Tanzania, incomplete adherence to therapy was associated with almost a three-fold increase in the odds of VF (20). In a study of ART outcomes among women in Johannesburg, South Africa, El-Khatib et al. found a significant association between having a viral load greater than 400 copies/mL (their definition of VF) and ever having an adherence level below 80% or 70% (16). Among people previously exposed to ARVs, the adherence threshold for VF may be higher than with ARV-naïve patients. Among women who had received sdNVP, VF was significantly associated with adherence levels less than 95%, indicating that even high adherence levels are risky for patients previously exposed to ARVs (16).

Risk Factors for Virological Failure

Gender, Age, and Duration of Antiretroviral Therapy

The association between gender, age, duration of ART and HIV treatment outcomes has already been established. Several studies have shown that men have worse HIV treatment outcomes than women. Men have higher mortality rates, medication and appointment adherence, worse virological outcomes, and greater loss to follow-up. In rural South Africa, a study found that male gender is associated with treatment failure in univariate and multivariate analysis, controlling for BMI, Karnofsky score, CD4 count and stavudine use (23). A systematic review and meta-analysis of the risk of death among ART enrollees in Africa found the risk of death in men was significantly higher than that in women (31). A longitudinal study of HIV treatment outcomes in Tanzania found men had significantly worse HIV and ART outcomes than women (32). Men in this study were at a higher risk of overall mortality and early mortality than women, and were more likely to have a CD4 cell count <100 cells/μl after six months on treatment (32). In a study of ART in Khayelistsha, South Africa, mortality rates among men were higher after three months on ART, and men had significantly lower CD4 cell count changes than women (24).

Part of the reason for the gender disparity in HIV outcomes could be that many HIV health services in Africa focus on maternal and child health issues, which target women (31, 33). Women thus have greater access to HIV and ART services during the key reproductive years, when HIV risk is the greatest (34). Women may also receive treatment at earlier stages of HIV, which has implications for good treatment outcomes. Because HIV in men is often detected later because of the lack of accessing services, men are more likely to start ART with more advanced HIV disease, reducing the likelihood of treatment success (33, 34). In Durban, South Africa, men were 1.66 times more like to present with late-stage HIV disease presentation than females (35). In KwaZulu-Natal, men initiated treatment at a higher age than women, with a lower CD4 cell count, and with a higher prevalence of tuberculosis (3). Also, men are more likely to be non-

adherent to treatment and care than women, possibly because women may have more experience with regular medication (contraceptives or supplements during pregnancy), or resulting from higher rates of alcohol abuse among men (34). Men in South Africa have higher rates of migratory work in mining and agriculture, which can impact their adherence, access to care, and social support (36). Men are also more likely to be lost to follow-up while on ART (32, 33). These gender disparities in ART usage are evident in South Africa, where approximately 55% of people living with HIV are women, but over two-thirds of those on public sector ART are women (33).

Several studies have established an association between age and ART treatment outcomes. The effect of age can be inconsistent, but outcomes and adherence tend to be poorest in the lowest age groups and highest age groups. In one study in rural South Africa, non-compliance with ART was highest in the 18-28 age group, and lowest in those older than 48 (37). Weintrob et al. found that older age at seroconversion in a US military cohort led to a shorter time suppression the virus while on ART and a longer time to a loss of viral response (38). In British Columbia, Canada, a younger age was associated with a higher probability of viral rebound after viral suppression on ART (28). Younger people may have poorer adherence, and thus worse virological outcomes, stemming from peer stigma and discrimination and multiple social distractions.

Age is also important in terms of HIV mortality rates. Older people are more likely to die and to experience slower CD4 responses because of the effects of aging on the immune system. Boulle et al. found that in Khayelistsha, South Africa, mortality rates after 3 months on therapy among patients older than 50 were 2.3 times that of younger patients, and younger patients (16-24) were twice as likely to experience VF (24).

Studies have also found an association between treatment duration and virological success. The longer a patient is on treatment, the less likely they are to experience virological failure. In British Columbia, Canada, Lima et al. found that regardless of adherence level, the

odds of viral rebound decrease by 8% per month of viral suppression on average (28). The probability of a viral rebound declined for all adherence levels from 12 months suppressed to 72 months suppressed, though the overall probability of rebound was less for those with greater adherence (28). In San Francisco, California, virological failure (in this study defined as a HIV RNA >50 copies/mL) was found to be associated with a shorter duration of viral suppression (29). The association between treatment duration and virological success on ART may be due in part to higher ARV medication levels needed to initially achieve viral suppression than to maintain suppression long-term and also to a smaller reservoir of replication competent virus over time on ART such that small interruptions in treatment do not result in virologic rebound (29).

Psychosocial Factors

Social Support and Stigma

Social capital, which includes trust, cooperation, reciprocity and sociability, may have implications for adherence success in sub-Saharan Africa (39). The desire for social capital and its preservation may underlie aspects of HIV risk and adherence in this setting (39). Social support, which involves assistance from a person's social network, including their family, friends, neighbors, and coworkers, is an important factor and influence in managing a chronic infection like HIV (40, 41). Social support, or lack of social support, can have an effect on accessing and adhering to HIV services and treatment. Therefore, recommendations for patients who initiate ART include provisions for social support, including disclosure of HIV status to at least one friend or family member, or to join an HIV support group (4).

The meaning and effect of social support is complex, and can depend on the culture and context of the person of interest. Social support can influence the emotional state of people living with HIV. In South Africa, people have many family members in their social network, and thus they may receive more support if they disclose their HIV status within supportive relationships (41). In a study of predominantly Zulu people receiving treatment for HIV/AIDS found that the

greater sense of social support was significantly associated with the number of close friends and family an individual had (41). Having more people in their network that they could rely on improved a person's sense of social support (41). One study of adherence among HIV patients in KwaZulu-Natal found an association between higher adherence and higher quality of life scores relating to general health perception and social relationships, and higher social support scores (42).

Social support achieved through relationships can also affect HIV treatment through medication adherence. In a study of treatment outcomes among women in South Africa, reporting a divorce or separation during the first 24 weeks on ART was marginally significantly associated with incomplete adherence (defined as ever returning more than 5% of pills at any visit within the 24 weeks) (16). Another study looking at adherence to ART found higher rates of non-adherence among men and women who were single, and married people tended to be more adherent (though this was seen more among women than men) (37). Along the same lines, disruptions in social support, as with death, family conflict, relationship disruption, may have implications on a patients desire to adhere (40). In a study of ART users in Cameroon, patients who reported having a main sexual partner but not live as a couple were more likely to be non-adherent than those who lived in a couple (43). In contrast, another study of adherence among HIV patients in KwaZulu-Natal found better adherence (measured using a 30-day visual analog scale [VAS]) in participants who were single, separated, divorced or widowed compared to those who were married and cohabiting (42). In this study, relationship and cohabiting inhibited medication adherence, showing how the impact of relationships and relationship disruptions on adherence is complicated.

Support is important to patients living with ART in a variety of ways, and the need for support can change as HIV treatment and symptoms change. According to qualitative research by Nachega et al. in Cape Town, South Africa, short-term support after an HIV diagnosis from clinic staff was important to HIV treatment adherence. Education and adherence counseling are

important at initiation of ART to influence treatment outcomes (4). Long-term support on ART depends more on social support than clinical staff support, and this shift is important to ensure long-term treatment success (4). This long-term social support can come in a variety of forms: a family member who assists in taking medication on time, or helps with access to medication, or having a friend also infected with HIV who provides mutual support (4).

According to Nachega et al., treatment supporters are crucial to maintaining long-term support (4). Treatment supporters are non-clinical people that a patient selects to assist with treatment adherence through dosage reminders, transportation funds, and other means (39). They can provide support in a variety of ways, through financial and material support, instrumental or logistical support like transportation to the clinic, and moral or emotional support (4). Nachega et al. identified the key qualities necessary in an effective treatment supporter: proximity to the patient, involvement on an emotional level, willing to listen, and treatment supporter must have authority (4). In Nachega's study, treatment supporters were most likely to be family members (4). Treatment supporters are important to assist patients in taking their medication (reminders, accessing medication), but also important to their psychological wellbeing (4).

In a qualitative study of HIV-infected patients, treatment supporters, and health-care workers, Ware et al. found that treatment supporters can also help to destigmatize HIV/AIDS because they socialize with HIV-infected people in public, and treatment supporters viewed HIV/AIDS as a more common and less stigmatized condition (39). Having treatment supporters, family, friends and providers who expected and required adherence from a patient encouraged the patient to maintain adherence to reduce their burden and show appreciation for their support (39). A positive feedback loop exists where patients want to maintain their adherence and health to maintain their social relationships, which then ensures that social relationships will exist moving forward to improve their long-term adherence (39). In another qualitative study of people living with HIV and their treatment partners, O'Laughlin et al. found that treatment partners encourage disclosure, combat stigma, restore hope and reduce social difference in the person they support

(44). Through these methods, treatment supports help to restore social connections and reduce social isolation among people living with HIV (44).

Studies have indicated that disclosure of HIV infection status can be associated with positive HIV treatment outcomes. In a study in Tanzania, disclosure was inversely associated with incomplete adherence and virological failure (cutoff of 400 copies/mL) and ARV drug resistance (20). In Nachega's qualitative study, disclosure of HIV status was cited as a key step in mobilizing social support (4). In ART users in Botswana, Do et al. found a significant association between not disclosing positive HIV status and non-adherence to ART (45). Because disclosing HIV status allows for the possibility of social support from others, people living with HIV who have disclosed tend to have better adherence than those who do not disclose (40).

However, disclosure among people living with HIV is complicated. There is often a reluctance to disclose one's HIV status because of the fear of stigma, and the possibility of rejection and other people sharing that information with others. People fear stigma because it can reduce social capital and lead to social isolation (39). In KwaZulu-Natal, fear of stigma and discrimination from disclosure of illness is a concern for people living with HIV/AIDS (41). Experiencing discrimination was associated with lower adherence scores in a study in Kwazulu-Natal (42). Many patients fear acceptance and anonymity if they tell others (4). In Soweto, South Africa, a study showed that fear of stigma from their partner was significantly associated with poor adherence in ART users (46). This fear and lack of disclosure can lead to ART users hiding their medication or skipping doses so others do not see (46). A qualitative study of patient advocates in South Africa found that patients who feared stigma and rejection from their family from disclosing their HIV status would not take their medications openly in front of their family (47). Even if the patient had disclosed their status to family, they may still not openly take medication because of shame and guilt (47).

In addition, functional status can be related to receiving social support. People with co-morbidities associated with HIV have reported lower social support, possibly because of their diminished functioning compared to others (41).

Faith and Spirituality

The association between faith, adherence, and virological success is not clear. In Kwazulu-Natal, a study found higher adherence scores using VAS among HIV patients with lower scores in the spirituality domain of a quality of life scale (42), implying that higher adherence is associated with less spirituality. However, another study assessing religiosity and adherence in Uganda found that religiosity and ART adherence were positively correlated (48).

Other studies have found that religion can be a barrier to adherence and proper ART use. A qualitative study of patient advocates in South Africa identified issues with Charismatic church and church leaders, in particular. They found that some church leaders urged patients to use prayer to overcome illness rather than the clinical treatments prescribed (47). Some church leaders saw ART use and adherence as a lack of faith in God (47). The patient advocates interviewed stated that sometimes patients would discontinue ART after receiving spiritual healing because they believed that they no longer needed medical treatment (47). An earlier prospective study in Uganda found that 1.2% of patients discontinued ART because of spiritual healing beliefs, all of whom were members of evangelical churches (49). The discontinuation of treatment led to mortality and tuberculosis relapse in these patients (49).

Alcohol and Drug Use

Substance abuse can impact adherence by impairing memory, concentration and physical coordination, as well as through its associations with mental health issues that may affect adherence (40). People who abuse alcohol and other drugs are often the same people who do not follow other healthy living recommendations. In addition, because of treatment guidelines to

avoid alcohol, people who abuse alcohol may delay or avoid treatment (50). Estimates of substance abuse prevalence in sub-Saharan Africa vary. One study estimated prevalence of abuse or dependence on alcohol and other substances to be between 7% and 16% among people living with HIV in sub-Saharan Africa (51).

Many studies have shown a relationship between substance abuse and medication adherence. A meta-analysis assessing adherence in sub-Saharan Africa found alcohol use prevalence rates between 2.5% and 51% (51). In the meta-analysis, Nakimuli-Mpungu et al. found associations between alcohol use and abuse and poor adherence, concluding that HIV positive individuals with alcohol problems may be at an increased risk for poor ART outcomes (51). Among patients receiving ART in Botswana, active alcohol use was significantly related to non-adherence (45). In a study of adherence in five African countries, never drinking alcohol in the past month was significantly associated with high adherence (52). In rural South Africa, higher rates of poor adherence with ART medication was found among men and women who drank alcohol (37). A study by Boyer et al. among patients on ART in Cameroon found that compared with adherent patients (self-reported), non-adherent patients and those with treatment disruption were more likely to report binge drinking (43). The relationship between alcohol use and poor adherence extends to resource-rich countries. In a study of medication adherence in HIV-positive persons, mostly men, on ART in urban Philadelphia, participants with high adherence were more likely to report no current alcohol or other drug use than participants with low adherence (53).

Depression

The presence of depression can have severe implications on the treatment success of people living with HIV on ART. Several studies have shown an association between depression and HIV incidence, accessing treatment, and treatment outcomes. Symptoms of depression include low motivation, poor concentration, sleep disturbance, fatigue, and feelings of

worthlessness, all of which can affect medication and clinic appointment adherence among HIV-positive people on ART (40).

Because of the variety of scales and measurements used to assess depression, estimates of the prevalence of depression among HIV-positive individuals vary. A meta-analysis of studies in sub-Saharan Africa found a pooled estimated prevalence of depressive symptoms of 31.2% among HIV-positive patients and an 18% prevalence of major depression (51). In a study of ART users in five African countries (not including South Africa), Etienne et al. found a prevalence of 20.8% with a high or severe depression score (52). The prevalence of psychological symptoms (being sad, irritable, worrying, and feeling nervous) among HIV-positive patients is even higher, with over 48% of South Africans attending HAART clinics in one study reporting high frequency of each symptom (54).

Regardless of the exact prevalence of depression, many studies have shown a significant association between depression and adherence among people on ART. In a meta-analysis of depression in sub-Saharan Africa, Nakimuli-Mpungu et al. found that achieving good adherence was 55% less likely among ART users with depression symptoms, which has implications on the effectiveness of ART in depressed patients (51). In KwaZulu-Natal, adherence was observed to be lower among participants with higher CES-D depression scores (42). Do et al. found a significant association between the presence of depression and non-adherence to ART among patients in Botswana (45). Ettiene et al. found an association between high depression scores and poor adherence in a study of adherence predictors in 5 African countries (52). Wagner et al. assessed the association of depression and HIV medication adherence by merging longitudinal data from 14 sites involved in the Multi-site Adherence Collaboration on HIV (MACH14). Overall, they found that adherence (measured using electronic data monitoring caps) was negatively correlated with depression, and those with good adherence have significantly lower depression than those with poor adherence (55). Depressive symptoms can impact other aspects of life for people living with HIV. In a study in Durban, South Africa, people with poor emotional

health were more likely to be diagnosed with late-stage HIV disease, which can lead to poor treatment outcomes (35).

Specific depressive symptoms may have a differential impact on adherence. Wagner et al. assessed the difference between vegetative symptoms (fatigue, loss of appetite or weight, sleep disturbance, and psychomotor agitation) and cognitive symptoms (depressed mood, loss of interest, suicidality, irritability, hopelessness, indecisiveness, poor concentration, worthlessness and guilt) (55). They found that most of the cognitive symptoms were significantly associated with non-adherence, and fatigue was the only vegetative symptom significantly associated with non-adherence (55). Many of the vegetative symptoms could be unrelated to depression, and instead be a result of medical illness, side effects and co-morbidities associated with living with HIV and being on ART (55).

The severity of depression could also have implications on how depressive symptoms impact adherence and ART outcomes. Wagner et al. found that severe depression affects adherence whereas mild and moderate depression do not (55). However, they did find that reduced depression over time is associated with improved adherence, which implies that interventions to improve depression among people on ART could improve their treatment outcomes (55).

Among people living with HIV, a variety of factors can be associated with having depressive symptoms. Symptomatic patients and those with lower functional ability tend to be at a greater risk of depression. Depressive symptoms have been found to be significantly more prevalent among symptomatic HIV patients that HIV-negative controls, and having increased HIV-related symptoms is associated with poorer quality of life and increased anxiety (56). In a study of health-seeking behavior among HIV-positive patients at McCord Hospital, lower functional activity scores were associated with an increase in depressive symptoms (9). In a meta-analysis of depression in developing countries, depression was associated with fatigue and lower scores on psychological, social, and environment scales of quality of life (56). At McCord

Hospital, older age, more education, and not living with your partner were significantly associated with depression (9).

Studies have used a variety of depression scales to assess prevalence and impact of depression in HIV-positive populations. Studies have used the Beck Depression Inventory (BDI) to assess the associations with medication adherence in Botswana (45), Mental Health Inventory (MHI-5) to look at risk factors for late-stage HIV disease in Durban, South Africa (35), Centers for Epidemiological Studies Depression Scale (CES-D) to assess treatment adherence in KwaZulu-Natal (42). A study of predictors of HIV treatment outcomes in Tanzania used the Hopkins Symptom Checklist-25 for depression and anxiety assessment, which had been previously validated in East Africa (20). Another study compiled information from 16 different studies using Beck Depression Inventory version II (BDI-II), Center for Epidemiological Studies Depression Scale (CES-D), and Brief Symptom Inventory (BSI) (55). They standardized the scales, and then calculated mean vegetative and cognitive subscales of depression symptom type.

The Kessler-10 measure has had mixed results in South Africa, with some studies finding a large number of patients with good internal reliability and substantial participants with a disorder in a KZN township, while another found it “acceptable” for screening depression among pregnant women in Cape Town, identifying 66% of major depressive cases (57, 58). When Kessler-10 validity was assessed in a nationally representative household study in South Africa, Andersen et al. found that it was less effective than in other settings, and had significantly worse discriminating ability among blacks than white, colored, Indian or Asian groups combined (59). Differing scores may result from differing interpretation or expression of depressive symptoms among black South Africans (59).

Chapter II: Manuscript

Title/Authors/Abstract

Title

Psychosocial Associations with Virological Failure among Patients on Antiretroviral Therapy at McCord Hospital in KwaZulu-Natal, South Africa

Authors

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Objective

Understanding factors associated with virological failure may improve prevention, diagnosis and treatment of virological failure among patients on ART.

Design

The RFVF is a study of cases with virological failure (VL > 1,000 copies/ML) and controls with virological suppression (VL ≤ 1,000 copies/ML) after at least 5 months on their first ART regimen at McCord Hospital in Durban, South Africa between October 2010 and June 2012.

Methods

Patients completed a questionnaire on medical history, psychosocial factors, depression using Kessler-10, and socioeconomic status, retrospective chart reviews were completed, and drug resistance genotyping was performed on cases. Using multivariate logistic regression, this sub-study assessed the significance of psychosocial factors on virological failure among the full study population, men and women separately.

Results

158 cases and 300 controls were enrolled in the study. The sample was predominantly female (64.6%), black Zulu (92%), and Christian (85.8%). In multivariate analysis for the full sample, male gender (OR=2.42, 95% CI 1.51-3.88), younger age (OR=0.83, 95% CI 0.72-0.94), shorter duration of treatment (OR=3.83, 95% CI 2.06-7.13 shortest vs. longest quartile) reporting any depressive symptoms (OR=2.21, 95% CI 1.35-3.61), being not active or having no faith compared to being somewhat or very active in faith (OR=1.60, 95% CI 1.02-2.50), having unsafe sex in prior 6 months (OR=2.50, 95% CI 1.17-5.32), having one or more HIV positive partner or family member (OR=1.70, 95% CI 1.03-2.82), having a treatment supporter (OR=2.02, 95% CI 1.13-3.64), and disclosing HIV status to friends (OR=2.02, 95% CI 1.23-3.33) were associated with virological failure. Among men, having at least one family member who died of HIV (OR=2.98, 95% CI 1.29-6.91) was also significantly associated with virological failure.

Conclusions

Several psychosocial factors are associated with virological failure in this setting. Patients experiencing failure were more likely to have a treatment supporter and family with HIV, depressive symptoms, have no active faith, have unsafe sex, and disclose their status to friends. Future studies should employ a longitudinal design to assess causality and ideally improve screening and identification of virological failure.

Introduction

South Africa has more people living with HIV/AIDS than any other country in the world, with an estimated 5.6 million people in 2009, of which 5.3 million were adults over the age of 15 (1). Women are estimated to make up the majority of people living with HIV/AIDS, accounting for 3.3 million, or 62% of prevalent cases (1). Anti-retroviral treatment (ART) can drastically improve morbidity and mortality among people living with HIV/AIDS. In 2004, ART became available through the government free of charge, and South Africa now has the largest public-sector ART program in the world (3, 4).

Despite the increase in treatment availability, continued success of ART depends on effective monitoring and treatment of HIV patients with virological failure (VF). Rapid scale-up of ART availability in sub-Saharan Africa presents new challenges in HIV care, including identifying and managing virological failure to maintain lifelong ART therapy for HIV patients. An estimated 4.9% to 19% of patients on first-line ART experience VF, using varying viral load thresholds (15, 19, 22-24). Even though only a small percentage of ART users experience VF, because of the size of the HIV epidemic in South Africa, VF affects a large number of people. As more patients in South Africa gain access to ART each year, more newly infected individuals initiate treatment, and patients stay on treatment for longer periods of time, virological failure will be a growing problem.

To improve treatment outcomes and care among HIV-positive patients, it is important to identify virological failure and, if necessary, switch patients to second-line regimens that may be more effective. However, it is difficult to diagnose and manage virological failure in resource-limited settings in sub-Saharan Africa (18). Many resource-poor settings lack the laboratory resources and technology required to accurately diagnose and manage VF, including CD4-lymphocyte count, plasma HIV RNA concentration, and drug-resistance profiles (18). These laboratory procedures can measure viral loads necessary to diagnosis VF, and identify major resistance to ARTs that can inform whether to switch therapies and if so, which ARVs to

prescribe. Routine viral monitoring is the gold standard for identifying VF (21). When patients with virological failure are not identified and managed accordingly, this can have a serious impact on treatment outcomes. If patients continue on a failing regimen, it could compromise their immunological and clinical state, as well as lead to replication of viruses with resistance to one or more antiretroviral drugs (15).

South Africa has standardized criteria for diagnosing virological failure. The South African Clinicians Society defines treatment failure using virological criteria; failure is a confirmed HIV viral load of >1,000 copies/mL in two measurements taken one to three months apart (13). The South African Department of Health guidelines mirror this criteria, with treatment switches only recommended when virological failure occurs, defined as a HIV viral load greater than 1,000 copies/mL (14). Unique among countries with high HIV burdens, South African ART programs implement routine viral load testing, with the South African National Department of Health recommending that patients on ART have viral load testing 6 months after ART initiation, 12 months after, and every subsequent 12 months (12, 21). Nonetheless, finding risk factors or methods to identify VF without viral load testing in South Africa could improve treatment outcomes in other settings without access to these tests.

Studies have found associations between several risk factors and HIV virological failure. Many studies have shown that men have worse HIV treatment outcomes than women, including higher mortality rates, medication and appointment adherence, higher rates of virological failure, and greater loss to follow-up (3, 23, 24, 31-35). Since men and women often have different experiences initiating and maintaining ART, it is important to consider risks separately by gender. Studies have shown ART outcomes and adherence tends to be poorest in the lowest age groups and highest age groups (where mortality rates are higher due to an aging immune system) (24, 28, 37, 38). Studies have also found an association between treatment duration and virological success. The longer a patient is on treatment, the less likely they are to experience virological failure (28, 29, 45).

Psychosocial factors likely have implications for ART success. The desire to obtain and maintain social capital, which includes trust, cooperation, reciprocity and sociability, may have a role in patient medication and appointment adherence in sub-Saharan Africa (39). Studies have assessed the role of marital/relationship status, disruptions in these relationships, treatment supporters, HIV-related stigma, and disclosure of HIV status on treatment adherence (4, 16, 37, 39, 40, 42, 44, 46). Results have varied, with disclosure being particularly complicated and dependent on culture and context. Several studies have shown that depression and having depressive symptoms are highly correlated with poor adherence among ART users (40, 42, 45, 51, 52, 55). Substance abuse can impact adherence by impairing memory, concentration and physical coordination, as well as through its associations with mental health issues that may affect adherence (40).

The relationship between faith and religiosity and ART adherence in South Africa has not been clearly established. Some have found that religion can be a barrier to ART adherence, while others have found that religiosity is positively correlated with ART adherence (47-49).

Many studies have assessed the association between psychosocial factors and adherence, but few have looked specifically at virological failure, which is not perfectly related to strong adherence among those on ART. This RFVF sub-study is an exploratory study to understand the importance of psychosocial characteristics in patients who experience virological failure. Understanding these factors can help direct future studies and create screening tools to identify patients on ART at risk of virological failure.

Methods

RFVF Study Methods

The Risk Factors for Virological Failure and HIV-1 Drug Resistance in Durban study (RFVF) is a density-type case control study set at McCord Hospital in Durban, South Africa. The purpose of the study is to identify predictors of virological failure and drug resistance in HIV-

positive patients and to study the emergence of HIV drug resistance mutations in this setting. To be eligible, all participants must have been 18 years or older, HIV positive, and receiving care at McCord Hospital or related clinics. Cases were defined as patients on their first ART regimen for ≥ 5 months who have a single viral load measurement of >1,000 copies/mL. Controls were defined as patients on their first ART regimen for ≥ 5 months with virological suppression (VL ≤ 1,000 copies/mL). As cases were identified at the HIV clinic and enrolled in the study, eligible controls were identified during the same week. Two controls were selected for each case, though they were not matched on any known predictors of virological failure. Enrollment and data collection began in October 2010 and ended in June 2012.

After enrollment, all participants completed a questionnaire in Zulu or English which collected information on medical and treatment history, symptoms, psychosocial factors (religion, spirituality, depression and anxiety using the Kessler-10 questionnaire, treatment supporters, alcohol and drug use, family members with HIV, experiences of abuse, stigma), socioeconomic status, transportation issues, alternative and traditional medicine use, and a functional assessment using the Karnofsky Performance Status Scale. A research assistant blinded to the case/control status of the participant administered the questionnaire in a semi-structured format. Retrospective chart review of all participants was completed to collect clinical information from the approximately 6 months prior to enrollment. A drug resistance genotype test was performed on all cases. Subsequent treatment decisions were based on current standards of care and not based on resistance type or preliminary results from this study. Patients were reimbursed 150 rand for their time participating in the study and for transportation.

Study data were collected and managed using REDCap electronic data capture tools hosted at Emory University (60). The study was approved through Emory University's Institutional Review Board and the McCord Research Ethics Committee.

Study Location

McCord Hospital is a state-funded hospital located in Durban, South Africa, the largest city in the KwaZulu-Natal (KZN) province. Sinikithemba Clinic is the outpatient HIV/AIDS clinic of McCord Hospital. Sinikithemba was established in 1998 to provide care to for HIV-positive patients and their families. In 2004, after receiving funding from the President's Emergency Plan for AIDS Relief (PEPFAR), Sinikithemba's ART program was expanded.(8) Currently, the clinic is subsidized by PEPFAR and the KZN Department of Health, and it is a regional referral center for ART (9, 10). The Sinikithemba clinic serves 3,000 to 4,000 adults per month, of which approximately 70% are black, Zulu speakers, 20% are Indian and 10% are white (9). The cost to attend the clinic is US $25 per visit (9). HIV care follows the guidelines outlined by the South African Department of Health, with HIV-1 viral load and CD4 cell count monitoring every 6 months (11). Adherence training and counseling is provided by the clinic prior to initiating ART and any time the patient has an elevated viral load measure (11).

Statistical Analysis

Variables on the Likert scale were assessed and categorized appropriately (for example, each Kessler-10 question was analyzed on both the Likert scale and subsets of categorization, and finally grouped by ever having the symptom versus never).

Univariate analyses of demographic and psychosocial variables were performed comparing those with (viral load >1000 copies/mL) and without virological failure (viral load < 1000 copies/mL) in the full sample, among women only, and among men only. For dichotomous or ordinal categorical variables, Fisher's exact test was used when the expected value for at least one of the subgroups was less than 5; otherwise, Pearson's chi-squared test was used. For nominal categorical variables, logistic regression was used with a class statement and referent group to obtain p-values. For numeric variables, two-sample t-tests were used to generate p-

values. Partner-specific questions were analyzed univariately with virological failure overall and by gender, including only those participants who reported having one or more current partners.

Multivariable logistic models predicting virological failure were run for three different cohorts: the full sample, women only, and men only. All variables with a univariate p-value less than 0.10 overall or by gender were considered in each model. Age at ART initiation and duration of ART were forced into all models, and gender into the overall model due to well-described associations with VF and adherence. When similar variables had significant univariate p-values, these variables were compared and appropriately narrowed down for inclusion in the initial logistic models. Multicollinearity was assessed before assessing each model. A backward selection process was used to identify the final logistic model. Variables in the multivariable model with a p-value less than 0.05 were removed one at a time until all remaining variables had a significant p-value. Likelihood ratio tests were performed when each variable was removed to assess whether the reduced model was significantly different than the full model.

All data were analyzed using SAS 9.3.

Results

Characteristics of Study Population

A total of 158 patients with virological failure and 300 controls without virological failure were identified and enrolled in the study. Demographic characteristics of the sample are shown in Table 1. 64.6% of the sample was female. The average age at starting first ART was 37, and average duration on ART at enrollment was 2.54 years. The sample was predominantly black Zulu (92%), and Christian (85.8%). 53.1% had completed education through grade 12 or higher and 78.6% had an income at enrollment. Few participants met the requirements of having clinical depressive disorder, but 66.8% reported experiencing depressive symptoms in the month prior to enrollment.

Univariate Analysis

Results from univariate analysis among the full sample are shown in Table 1. In univariate analysis, cases were significantly more likely than controls to be male (47.5% vs. 29.0%; p<0.0001), start their first ART regimen at a younger age (34.9 vs. 38.1; p=0.000), have been on ART for a shorter duration (2.11 vs. 2.77 years; p=0.001), to have completed more schooling (58.9% vs. 50.0% completed grade 12; p=0.015 with completing grades 0-7 as reference group), and have depressive symptoms (74.7% vs. 62.7%l p=0.009). Cases were significantly more likely than controls to have a partner or family members that is HIV positive (77.8% vs. 63.7%; p=0.002), to have more than one partner or family member with HIV (36.1% vs. 25.7%; p=0.005), to have a treatment supporter (22.6% vs. 11.5%; p=0.002), and to have one or more friends who know they have HIV (31.6% vs. 19.7%; p=0.004). Cases were significantly less likely than controls to have an income (72.2% vs. 82.0%; p =0.015), have a religious faith (82.9% vs. 91.3%; p=0.007) and be active in that faith (39.2% vs. 58.3%; p=0.000). Cases were less likely than controls to always practice safe sex in the 6 months prior to enrollment (84.7% vs. 95.0%; p<0.0001), and to have no current partners (26.6% vs. 39.3%; p=0.014). Alcohol use was not significantly associated with virological failure (14.6% in cases vs. 11.3% in controls; p=0.321).

When comparing the association of psychosocial factors and virological failure by gender, one additional factor was associated with virological failure among men (Table 2 and Table 3). Male cases were more likely to have one or more family member who has died of HIV compared to male controls (37.3% vs. 18.4%; p=0.007).

Among participants with partners, the only partner-specific question that was significantly associated with virological failure was the likelihood of always practicing safe sex in the 6 months prior to enrollment (overall: 79.1% vs. 91.8%; p=0.002, females: 75.0% vs. 89.3%; p=0.020, males: 82.1% vs. 95.7%; p=0.011). See Table 4.

Multivariate Analysis

Results from the multivariate analysis are shown in Table 5. In multivariable logistic models, the following variables were significantly associated with virological failure in the overall sample: male gender (OR=2.42, 95% CI 1.51-3.88), younger age (OR=0.83, 95% CI 0.72-0.94 for increasing 5 year age groups), shorter duration of treatment (OR=3.83, 95% CI 2.06-7.13 for those in the first quartile of treatment duration, ≤0.83 years, compared to those in that last quartile of treatment duration, ≥3.58 years) reporting any depressive symptoms (OR=2.21, 95% CI 1.35-3.61), being not active or having no faith compared to being somewhat or very active in faith (OR=1.60, 95% CI 1.02-2.50), not always practicing safe sex in the 6 months prior to enrollment (OR=2.50, 95% CI 1.17-5.32), having at least one HIV positive partner or family member (OR=1.70, 95% CI 1.03-2.82), having a treatment supporter (OR=2.02, 95% CI 1.13-3.64), and having one or more friends know their HIV status (OR=2.02, 95% CI 1.23-3.33).

In the gender-specific multivariable analysis, different factors were significant for men and women. Among women, younger age (OR=0.77, 95% CI 0.65-0.91 for increasing 5 year age groups), shorter duration of treatment (OR=4.13, 95% CI 1.82-9.40 for those in the first quartile vs. last quartile of treatment duration), reporting any depressive symptoms (OR=2.42, 95% CI 1.23-4.77), being not active or having no faith compared to being somewhat or very active in faith (OR=1.75, 95% CI 1.00-3.06), and having a treatment supporter (OR=2.49, 95% CI 1.19-5.20) were all significantly associated with virological failure. Among men, shorter duration of treatment (OR=5.38, 95% CI 1.84-15.72 for those in the first quartile vs. last quartile of treatment duration), reporting any depressive symptoms (OR=2.40, 95% CI 1.13-5.11), having at least one HIV positive partner or family member (OR=2.44, 95% CI 1.01-5.90), having at least one family member who died of HIV (OR=2.98, 95% CI 1.29-6.91), and having one or more friends know their HIV status (OR=3.67, 95% CI 1.46-9.23) were all significantly associated with virological failure.

Discussion

The associations between gender, age and duration on ART and virological failure found in this study are consistent with existing literature (3, 23, 24, 28, 29, 31-35, 37, 38, 45). As described in many other studies in sub-Saharan Africa, males experience worse virologic outcomes than women, with an almost 2.5 times greater odds of virological failure than women. Several factors likely play into this gender disparity. Many HIV health services in Africa focus on maternal and child health, which target women and often identify HIV and provide treatment at earlier stages of infection leading to better overall treatment outcomes (31, 33). Since HIV in men is often detected later because of the lack of accessing services, men often start ART with more advanced HIV disease, reducing the likelihood of treatment success (3, 33-35). Men are also more likely to be lost to follow-up and be non-adherent to treatment and care than women, possibly because women may have more experience with regular medication (oral contraceptives or supplements during pregnancy), or resulting from higher rates of alcohol abuse among men (32-34). Men in South Africa also have higher rates of migratory work in mining and agriculture, which can impact their adherence, access to care, and social support (36). These gender disparities in ART usage are evident in South Africa, where approximately 55% of people living with HIV are women, but over two-thirds of those on public sector ART are women (33).

The associations between younger age at initiating ART and a shorter duration of ART and virological failure have been found in other studies. Younger people may experience increased peer stigma and discrimination, and face multiple social distractions, leading to worse adherence and thus virologic outcomes. A study in British Columbia, Canada, found that regardless of adherence level, the odds of viral rebound decrease by 8% per month of viral suppression on average (28). The association between treatment duration and virological success on ART may be due in part to higher ARV medication levels needed to initially achieve viral suppression than to maintain suppression long-term and also to a smaller reservoir of replication-

competent virus over time on ART such that small interruptions in treatment do not result in virologic rebound (29). Another explanation is that patients have improved adherence rates after being on treatment for longer.

This analysis identified several psychosocial factors associated with virological failure at McCord Hospital. Depressive symptoms are associated with virological failure in all three models. A meta-analysis of depression studies in sub-Saharan Africa found that achieving good adherence was 55% less likely among ART users with depression symptoms (51). In separate studies in KZN, Botswana, and another in 5 African countries, adherence was lower among participants with higher depression scores (42, 45, 52). A study using longitudinal data from 14 sites involved in the Multi-site Adherence Collaboration on HIV (MACH14) found that adherence was negatively correlated with depression, and those with good adherence have significantly lower depression than those with poor adherence (55). Thus, the findings in this analysis are consistent with prior research.

While many participants reported having depressive symptoms, few met the traditional thresholds for clinical depression on the Kessler-10 scale. Only 4.4% of the study population met the threshold for any depressive disorder, which is much lower than other prevalence estimates of 20-31% in sub-Saharan Africa (51, 52). It is unclear whether this stems from a lack of clinical depression in this population, or whether the Kessler-10 scale is not a sensitive enough tool to measure depression in this setting. The Kessler-10 measure has had mixed results in South Africa, with some studies finding a large number of patients with good internal reliability and substantial participants with a disorder a KZN township, while another found it “acceptable” for screening depression among pregnant women in Cape Town, identifying 66% of major depressive cases (57, 58). When Kessler-10 validity was assessed in a nationally representative household study in South Africa, Andersen et al. found that it was less effective than in other settings, and had significantly worse discriminating ability among blacks than white, colored, Indian or Asian

groups combined (59). Differing scores may result from differing interpretation or expression of depressive symptoms among black South Africans (59).

In this analysis, not always practicing safe sex in the 6 months prior to study enrollment was associated with experiencing virological failure in the overall population. This was not significant among men or women individually, likely due to small sample sizes once the data was stratified by gender. A similar association between sub-optimal adherence and inconsistent condom use was observed in a longitudinal study in Cameroon (61). This question may also be a proxy for patients with a "risk taking personality" or who have other behaviors associated with virological failure (62). A study among woman in the U.S. found an association between higher scores in risk behavior scales, including questions on frequency of safe sex, and low levels of adherence (62). To better understand sexual risk among HIV-infected people in this setting, future studies should include more specific questions on sexual behavior.

Not having a faith and not being active in one's faith and having a treatment supporter were associated with virological failure among women, but not among men individually. Both factors involve a structured social network, whether it is organized religion or a pre-determined treatment partner. Studies have shown that faith can play conflicting roles in ART adherence in sub-Saharan Africa. If religion serves as a network of social support, it may improve psychological wellbeing and thus play a positive role in ART adherence. A study in Uganda found that religiosity and ART adherence were positively correlated (48). However, other studies have found that religion can be a barrier to adherence and proper ART use. A qualitative study of patient advocates in South Africa found that some church leaders urged patients to use prayer to overcome illness rather than prescribed clinical treatments, and that sometimes patients would discontinue ART after receiving spiritual healing because they believed that they no longer needed medical treatment (47). Since our study did not include patients who dropped out of care, we likely would not see this phenomenon as these patients have already decided in favor of staying with Western medicine and ART. Another study in Uganda found that 1.2% of patients

discontinued ART because of spiritual healing beliefs, all of whom were members of evangelical churches (49). Nonetheless, religiosity and being active in faith seems to have a positive role in virological success in this setting, particularly among women.

Having a treatment supporter was associated with experiencing virological failure. This association could stem from patients who begin experiencing symptoms of virological failure or have poor adherence. They may be more likely to identify a treatment supporter or to be encouraged by a clinician to do so. While the order of events is unknown in this study, the association between having a treatment supporter and virological failure is inconsistent with most literature. According to Nachega et al., treatment supporters are crucial to maintaining long-term support (4). They can provide support in a variety of ways, through financial and material support, instrumental or logistical support like transportation to the clinic and reminders and assistance in taking medication, and moral/emotional support (4). Treatment supporters can help to destigmatize HIV/AIDS because they socialize with HIV-infected people in public, can restore hope and reduce social difference in the person they support, and reduce social isolation among people living with HIV (39, 44). Patients want to maintain their adherence and health to maintain relationships with their treatment supporters, which then ensures that social relationships will exist moving forward to improve their long-term adherence (39).

Several variables related to social and family relationships were associated with virological failure among men but not women: having a friend know you have HIV and having family members who are HIV positive or have died from HIV. Men may be more affected by family members being HIV-positive or dying of HIV because he might feel responsible for their infection, particularly if it is a partner or child. When HIV inhibits a man's ability to maintain employment or care for the family, they may feel more guilt and low self-esteem from "failing" their family, leading to disclosure or treatment issues (50). Additionally, men tend to be more nervous of the physical symptoms of HIV than females, so seeing family members suffer from HIV infection and death may affect his coping, depression, and thus immune response. (Sally

John, personal communication) It is also possible that having a family member, particularly a partner, who has died from HIV is a marker of having a longer term infection, and if treatment was not initiated early, could lead to poor treatment outcomes and virological failure.

Disclosing HIV status to friends, by choice or not, could lead to increased stigma, and thus worse adherence and treatment outcomes. There is often a reluctance to disclose one's HIV status because of the fear of stigma, and the possibility of rejection, other people sharing that information with others, and social isolation (39, 41). Having experiences of discrimination were associated with lower adherence scores in a study in KZN (42). In KZN, men fear disapproval and being made fun of by other men if they disclose their status (50). Studies in South Africa have found that patients who fear stigma and rejection from their family or friends from disclosing their HIV status hide their medication, do not take their medication openly, and skip doses to avoid others from seeing (46, 47). Even if the patient had disclosed their status to family, they may still not openly take medication because of shame and guilt (47).

Limitations

Since the questionnaire was administered after patients had been diagnosed, the causal relationship of these associations cannot be established. Prior to enrollment, patients with virological failure may have experienced medical symptoms that could influence their psychosocial health and create issues that were not present prior to failing treatment. For example, symptoms of virological failure could lead participants to feel depressive symptoms, rather than those depressive symptoms leading to changes in adherence that could lead to virological failure. One of the most statistically significant Kessler-10 questions asked whether the participant felt tired during the last 4 weeks, and fatigue is prevalent among people on ART and is associated with a variety of other psychological and clinical factors (55, 63). Due to the cross-sectional nature of the study, it is unclear when a participant may have disclosed their HIV status to their partners, spouse, friends, or family, or when they might have established a

treatment supporter. If a participant failing treatment is experiencing clinical symptoms, it may force them to disclose their status when otherwise they may not.

In addition, participants knew their virological failure status at the time of enrollment, as was necessary to identify cases eligible for the study. This may have influenced some of their symptoms and answers to the questionnaire but likely not substantially.

Lastly, several of the estimates in this analysis are imprecise with wide confidence intervals. Future studies may require a larger sample size to confirm the associations and improve precision of psychosocial factors.

Conclusion

In conclusion, this analysis highlighted several key psychosocial factors that are important among patients experiencing virological failure in this setting. Future studies should employ a longitudinal design to better understand the chronology and causality of depression, social support, disclosure, and faith and virological failure and identify potential areas to improve treatment outcomes and psychosocial health among people living with HIV. As more people in South Africa and elsewhere stay on treatment for longer, it will become increasingly crucial to understand the nuances and risk factors of poor adherence and virological failure.

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Appendices

Tables

Table 1. Characteristics of study population overall and by case control status, McCord Hospital, Durban, SA, 2010-2012

Patient Characteristic	Overall (n = 458)	Cases (n = 158)	Controls (n = 300)	p-value†
Demographics				
Female Gender; n(%)	296 (64.6%)	83 (52.5%)	213 (71.%)	<0.0001
Male gender; n(%)	162 (35.4%)	75 (47.5%)	87 (29.%)	<0.0001
Age at starting first ART; mean (sd)	37.04 (8.96)	34.96 (8.26)	38.14 (9.14)	0.000
Black Zulu; n(%)	422 (92.1%)	151 (95.6%)	271 (90.3%)	0.048
Last grade of education; n(%)				
Grade 0 through 7	54 (11.8%)	11 (7.0%)	43 (14.3%)	ref
Grade 8 through 11	161 (35.2%)	54 (34.2%)	107 (35.7%)	0.071
Grade 12	243 (53.1%)	93 (58.9%)	150 (50.0%)	0.015
Has an income; n(%)	360 (78.6%)	114 (72.2%)	246 (82.0%)	0.015
Unemployed; n(%)	87 (19.0%)	39 (24.7%)	48 (16.0%)	0.024
Married/living with partner; n(%)	158 (34.5%)	59 (37.3%)	99 (33.0%)	0.353
HIV/ART Characteristics				
Treatment duration, years; mean (sd)	2.54 (2.06)	2.11 (2.11)	2.77 (2.00)	0.001
Treatment duration, quartiles ; n(%)				
<=0.83 years	115 (25.1%)	63 (39.9%)	52 (17.3%)	ref
0.83 - 2.05 years	114 (24.9%)	37 (23.4%)	77 (25.7%)	0.001
2.05 - 3.58 years	115 (25.1%)	28 (17.7%)	87 (29.0%)	<0.0001
3.58+ years	114 (24.9%)	30 (19.0%)	84 (28.0%)	<0.0001
CD4 count, cells/uL; n(%)*				
500 +	87 (19.1%)	17 (10.8%)	70 (23.4%)	<0.0001
350 - 500	105 (23.0%)	19 (12.1%)	86 (28.8%)	
200 - 350	138 (30.3%)	47 (29.9%)	91 (30.4%)	
<200	126 (27.6%)	74 (47.1%)	52 (17.4%)	
Depressive Symptoms				
K-10 scale, trad'l categories; n(%)				
Well (10-19)	437 (95.4%)	146 (92.4%)	291 (97.0%)	0.060
Mild disorder (20-24)	15 (3.3%)	9 (5.7%)	6 (2.0%)	
Moderate disorder (25-29)	5 (1.1%)	2 (1.3%)	3 (1.0%)	
Severe disorder (30-50)	1 (0.2%)	1 (0.6%)	0 (0.0%)	
Has any depressive symptoms	306 (66.8%)	118 (74.7%)	188 (62.7%)	0.009
Faith				
Religious Faith; n(%)				
No faith	53 (11.6%)	27 (17.1%)	26 (8.7%)	ref

Christian**	393 (85.8%)	125 (79.1%)	268 (89.3%)	0.007
Other	12 (2.6%)	6 (3.8%)	6 (2.0%)	0.953
Activity in faith; n(%)				
No faith/not active	221 (48.3%)	96 (60.8%)	125 (41.7%)	0.000
Somewhat/very active	237 (51.7%)	62 (39.2%)	175 (58.3%)	
Ever taken traditional meds; n(%)	264 (57.6%)	89 (56.3%)	175 (58.3%)	0.680
Partners/Sexual Practices				
Frequency of safe sex in last 6 months; n(%)				
Always	418 (91.3%)	133 (84.7%)	285 (95.0%)	0.000
Often, sometimes, rarely, never	39 (8.5%)	24 (15.3%)	15 (5.0%)	
Practices abstinence; n (%)	176 (38.4%)	45 (28.5%)	131 (43.7%)	0.002
Practices safe sex w condoms; n (%)	277 (60.5%)	109 (69.0%)	168 (56.0%)	0.007
Number of current partners; n(%)				
0	160 (34.9%)	42 (26.6%)	118 (39.3%)	0.014
1	292 (63.8%)	113 (71.5%)	179 (59.7%)	
2	6 (1.3%)	3 (1.9%)	3 (1.0%)	
Child Care and Family				
Has biological children; n(%)	393 (85.8%)	134 (84.8%)	259 (86.3%)	0.657
Has any children taking care of; n(%)	366 (79.9%)	121 (76.6%)	245 (81.7%)	0.197
Has HIV+ child; n(%)****	43 (11.7%)	17 (14.0%)	26 (10.6%)	0.337
Has HIV+ partner/family; n(%)	314 (68.6%)	123 (77.8%)	191 (63.7%)	0.002
Has family who died of HIV; n(%)	171 (37.3%)	61 (38.6%)	110 (36.7%)	0.683
Disclosure/Social Support				
Has a treatment supporter; n(%)	69 (15.1%)	35 (22.6%)	34 (11.5%)	0.002
Partner knows HIV status; n(%)	292 (63.8%)	113 (71.5%)	179 (59.7%)	0.012
Family knows HIV status; n(%)	401 (87.6%)	138 (87.3%)	263 (87.7%)	0.920
Friend(s) knows HIV status; n(%)	109 (23.8%)	50 (31.6%)	59 (19.7%)	0.004
Work knows HIV status; n(%)	48 (10.5%)	13 (8.2%)	35 (11.7%)	0.253
Ever drinks alcohol; n(%)	57 (12.4%)	23 (14.6%)	34 (11.3%)	0.321

*Missing CD4 count from 2 subjects

**One person reported from Christian and Traditional African

***Missing practicing safe sex data from 1 subject

****Includes only those that report a child in their care

†P-values obtained for categorical variables using Fisher's exact test (when expected value for at least one subgroup was less than 5), Pearson's chi-squared (if no expected values less than 5), or logistic regression (for 3+-level nominal variables). For numeric variables, two-sample t-tests were used.

Table 2. Characteristics of female study population overall and by case control status, McCord Hospital, Durban, SA, 2010-2012

Patient Characteristic	Overall (n = 296)	Cases (n = 83)	Controls (n = 213)	p-value†
Demographics				
Age at starting first ART; mean (sd)	36.43 (9.05)	33.41 (8.65)	37.6 (8.95)	0.000
Black Zulu; n(%)	272 (91.9%)	80 (96.4%)	192 (90.1%)	0.077
Last grade of education; n(%)				
Grade 0 through 7	35 (11.8%)	5 (6.%)	30 (14.1%)	ref
Grade 8 through 11	94 (31.8%)	25 (30.1%)	69 (32.4%)	0.148
Grade 12	167 (56.4%)	53 (63.9%)	114 (53.5%)	0.045
Has an income; n(%)	220 (74.3%)	53 (63.9%)	167 (78.4%)	0.010
Unemployed; n(%)	67 (22.6%)	26 (31.3%)	41 (19.2%)	0.026
Married/living with partner; n(%)	66 (22.3%)	15 (18.1%)	51 (23.9%)	0.276
HIV/ART Characteristics				
Treatment duration, years; mean (sd)	2.68 (2.09)	2.13 (1.95)	2.9 (2.11)	0.004
Treatment duration, quartiles ; n(%)				
<=0.83 years	64 (21.6%)	29 (34.9%)	35 (16.4%)	ref
0.83 - 2.05 years	78 (26.4%)	23 (27.7%)	55 (25.8%)	0.053
2.05 - 3.58 years	75 (25.3%)	17 (20.5%)	58 (27.2%)	0.005
3.58+ years	79 (26.7%)	14 (16.9%)	65 (30.5%)	0.001
CD4 count, cells/uL; n(%)*				
500 +	65 (22.0%)	10 (12.%)	55 (18.4%)	<0.0001
350 - 500	73 (24.7%)	12 (14.5%)	61 (20.4%)	
200 - 350	90 (30.4%)	24 (28.9%)	66 (22.1%)	
<200	68 (23.0%)	37 (44.6%)	31 (10.4%)	
Depressive Symptoms				
K-10 scale, trad'l categories; n(%)				
Well (10-19)	279 (94.3%)	74 (89.2%)	205 (96.2%)	0.051
Mild disorder (20-24)	12 (4.1%)	6 (7.2%)	6 (2.8%)	
Moderate disorder (25-29)	4 (1.4%)	2 (2.4%)	2 (0.9%)	
Severe disorder (30-50)	1 (0.3%)	1 (1.2%)	0 (0.0%)	
Has any depressive symptoms	177 (59.8%)	65 (78.3%)	112 (52.6%)	<0.0001
Faith				
Religious Faith; n(%)				
No faith	17 (5.7%)	6 (7.2%)	11 (5.2%)	ref
Christian**	278 (93.9%)	76 (91.6%)	202 (94.8%)	0.479
Other	1 (0.3%)	1 (1.2%)	0 (0.0%)	0.988
Activity in faith; n(%)				
No faith/not active	119 (40.2%)	45 (54.2%)	74 (34.7%)	0.002
Somewhat/very active	177 (59.8%)	38 (45.8%)	139 (65.3%)	

Ever taken traditional meds; n(%)	150 (50.7%)	37 (44.6%)	113 (53.1%)	0.190
Partners/Sexual Practices				
Frequency of safe sex in last 6 months; n(%)				
Always	271 (91.6%)	70 (84.3%)	201 (94.4%)	0.011
Often, sometimes, rarely, never	24 (8.1%)	12 (14.5%)	12 (5.6%)	
Practices abstinence; n (%)	148 (50.0%)	36 (43.4%)	112 (52.6%)	0.155
Practices safe sex w condoms; n (%)	145 (49.0%)	44 (53.0%)	101 (47.4%)	0.387
Number of current partners; n(%)				
0	135 (45.6%)	34 (41.0%)	101 (47.4%)	0.317
1	161 (54.4%)	49 (59.0%)	112 (52.6%)	
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Child Care and Family				
Has biological children; n(%)	246 (83.1%)	67 (80.7%)	179 (84.0%)	0.494
Has any children taking care of; n(%)	231 (78.0%)	61 (73.5%)	170 (79.8%)	0.238
Has HIV+ child; n(%)****	30 (13.0%)	11 (18.0%)	19 (7.8%)	0.172
Has HIV+ partner/family; n(%)	197 (66.6%)	64 (77.1%)	133 (62.4%)	0.016
Has family who died of HIV; n(%)	127 (42.9%)	33 (39.8%)	94 (44.1%)	0.495
Disclosure/Social Support				
Has a treatment supporter; n(%)	41 (13.9%)	21 (25.3%)	20 (9.4%)	0.000
Partner knows HIV status; n(%)	157 (53.0%)	46 (55.4%)	111 (52.1%)	0.608
Family knows HIV status; n(%)	277 (93.6%)	80 (96.4%)	197 (92.5%)	0.219
Friend(s) knows HIV status; n(%)	75 (25.3%)	28 (33.7%)	47 (22.1%)	0.038
Work knows HIV status; n(%)	33 (11.1%)	7 (8.4%)	26 (12.2%)	0.354
Ever drinks alcohol; n(%)	30 (10.1%)	12 (14.5%)	18 (8.5%)	0.124

*Missing practicing safe sex data from 1 subject

**Includes only those that report a child in their care

†P-values obtained for categorical variables using Fisher's exact test (when expected value for at least one subgroup was less than 5), Pearson's chi-squared (if no expected values less than 5), or logistic regression (for 3+-level nominal variables). For numeric variables, two-sample t-tests were used.

Table 3. Characteristics of male study population overall and by case control status, McCord Hospital, Durban, SA, 2010-2012

Patient Characteristic	Overall (n = 162)	Cases (n = 75)	Controls (n = 87)	p-value†
Demographics				
Age at starting first ART; mean (sd)	38.17 (8.72)	36.69 (7.86)	39.44 (9.52)	0.041
Black Zulu; n(%)	150 (92.6%)	71 (94.7%)	79 (90.8%)	0.349
Last grade of education; n(%)				
Grade 0 through 7	19 (11.7%)	6 (8.%)	13 (14.9%)	ref
Grade 8 through 11	67 (41.4%)	29 (38.7%)	38 (43.7%)	0.362
Grade 12	76 (46.9%)	40 (53.3%)	36 (41.4%)	0.107
Has an income; n(%)	140 (86.4%)	61 (81.3%)	79 (90.8%)	0.079
Unemployed; n(%)	20 (12.3%)	13 (17.3%)	7 (8.0%)	0.073
Married/living with partner; n(%)	92 (56.8%)	44 (58.7%)	48 (55.2%)	0.654
HIV/ART Characteristics				
Treatment duration, years; mean (sd)	2.28 (1.98)	2.08 (2.29)	2.45 (1.65)	0.257
Treatment duration, quartiles ; n(%)				
<=0.83 years	51 (31.5%)	34 (45.3%)	17 (19.5%)	ref
0.83 - 2.05 years	36 (22.2%)	14 (18.7%)	22 (25.3%)	0.012
2.05 - 3.58 years	40 (24.7%)	11 (14.7%)	29 (33.3%)	0.000
3.58+ years	35 (21.6%)	16 (21.3%)	19 (21.8%)	0.055
CD4 count, cells/uL; n(%)*				
500 +	22 (13.8%)	7 (9.5%)	15 (17.4%)	0.001
350 - 500	32 (20.%)	7 (9.5%)	25 (29.1%)	
200 - 350	48 (30.%)	23 (31.1%)	25 (29.1%)	
<200	58 (36.3%)	37 (50.%)	21 (24.4%)	
Depressive Symptoms				
K-10 scale, trad'l categories; n(%)				
Well (10-19)	158 (97.5%)	72 (96.%)	86 (98.9%)	0.097
Mild disorder (20-24)	3 (1.9%)	3 (4.%)	0 (.%)	
Moderate disorder (25-29)	1 (.6%)	0 (.%)	1 (1.1%)	
Severe disorder (30-50)	0 (.%)	0 (.%)	0 (.%)	
Has any depressive symptoms	75 (46.3%)	42 (56.%)	33 (37.9%)	0.022
Faith				
Religious Faith; n(%)				
No faith	36 (22.2%)	21 (28.%)	15 (17.2%)	ref
Christian**	115 (71.%)	49 (65.3%)	66 (75.9%)	0.101
Other	11 (6.8%)	5 (6.7%)	6 (6.9%)	0.454
Activity in faith; n(%)				
No faith/not active	102 (63.%)	51 (68.%)	51 (58.6%)	0.218
Somewhat/very active	60 (37.%)	24 (32.%)	36 (41.4%)	

Ever taken traditional meds; n(%)	114 (70.4%)	52 (69.3%)	62 (71.3%)	0.788
Partners/Sexual Practices				
Frequency of safe sex in last 6 months; n(%)				
Always	147 (90.7%)	63 (84.%)	84 (96.6%)	0.006
Often, sometimes, rarely, never	15 (9.3%)	12 (16.%)	3 (3.4%)	
Practices abstinence; n (%)	28 (17.3%)	9 (12.%)	19 (21.8%)	0.099
Practices safe sex w condoms; n (%)	132 (81.5%)	65 (86.7%)	67 (77.%)	0.115
Number of current partners; n(%)				
0	25 (15.4%)	8 (10.7%)	17 (19.5%)	0.289
1	131 (80.9%)	64 (85.3%)	67 (77.%)	
2	6 (3.7%)	3 (4.%)	3 (3.4%)	
Child Care and Family				
Has biological children; n(%)	147 (90.7%)	67 (89.3%)	80 (92.%)	0.566
Has any children taking care of; n(%)	135 (83.3%)	60 (80.%)	75 (86.2%)	0.291
Has HIV+ child; n(%)****	13 (9.6%)	6 (8.%)	7 (8.%)	0.896
Has HIV+ partner/family; n(%)	117 (72.2%)	59 (78.7%)	58 (66.7%)	0.089
Has family who died of HIV; n(%)	44 (27.2%)	28 (37.3%)	16 (18.4%)	0.007
Disclosure/Social Support				
Has a treatment supporter; n(%)	28 (17.3%)	14 (18.7%)	14 (16.1%)	0.666
Partner knows HIV status; n(%)	135 (83.3%)	67 (89.3%)	68 (78.2%)	0.057
Family knows HIV status; n(%)	124 (76.5%)	58 (77.3%)	66 (75.9%)	0.826
Friend(s) knows HIV status; n(%)	34 (21.%)	22 (29.3%)	12 (13.8%)	0.015
Work knows HIV status; n(%)	15 (9.3%)	6 (8.%)	9 (10.3%)	0.608
Ever drinks alcohol; n(%)	27 (16.7%)	11 (14.7%)	16 (18.4%)	0.526

*Missing CD4 count from 2 subjects

**Includes only those that report a child in their care

†P-values obtained for categorical variables using Fisher's exact test (when expected value for at least one subgroup was less than 5), Pearson's chi-squared (if no expected values less than 5), or logistic regression (for 3+-level nominal variables). For numeric variables, two-sample t-tests were used.

Table 4. Partner characteristics and sex practices among study participants who report a current partner, McCord Hospital, Durban, SA, 2010-2012

	Overall (n =298)			Females (n = 161)			Males (n = 137)		
Patient Characteristic	**Cases (n = 116)**	**Controls (n = 182)**	**p-value†**	**Cases (n = 49)**	**Controls (n = 112)**	**p-value†**	**Cases (n = 67)**	**Controls (n = 70)**	**p-value†**
	n(%)	n(%)		n(%)	n(%)		n(%)	n(%)	
Safe sex in last 6 months									
Always	91 (79%)	167 (92%)	0.002	36 (75%)	100 (89%)	0.020	55 (82%)	67 (96%)	0.011
Practices abstinence	3 (3%)	13 (7%)	0.089	2 (4%)	11 (10%)	0.347	1 (1%)	2 (3%)	1.000
Practices safe sex w condoms	109 (94%)	168 (92%)	0.586	44 (90%)	101 (90%)	1.000	65 (97%)	67 (96%)	1.000
Partner knows HIV status	111 (96%)	171 (94%)	0.517	45 (92%)	104 (93%)	0.757	66 (99%)	67 (96%)	0.620
Partner(s) tested for HIV	96 (83%)	154 (85%)	0.671	37 (76%)	91 (81%)	0.407	59 (88%)	63 (90%)	0.716
Lives with any partners	58 (50%)	97 (53%)	0.579	15 (31%)	51 (46%)	0.077	43 (64%)	46 (66%)	0.851
Partner HIV & ART Status									
HIV-negative partner	41 (35%)	67 (37%)	ref	23 (47%)	46 (41%)	ref	18 (27%)	21 (30%)	ref
HIV+ partner not on ART	37 (32%)	52 (29%)	0.606	13 (27%)	32 (29%)	0.618	24 (36%)	20 (29%)	0.446
HIV+ partner on ART	38 (33%)	63 (35%)	0.960	13 (27%)	34 (30%)	0.517	25 (37%)	29 (41%)	0.989

*Missing data from one person on practicing safe sex

†P-values obtained for categorical variables using Fisher's exact test (when expected value for at least one subgroup was less than 5), Pearson's chi-squared (if no expected values less than 5), or logistic regression (for 3+-level nominal variables). For numeric variables, two-sample t-tests were used.

Table 5. Psychosocial characteristics associated with HIV virological failure, McCord Hospital, Durban, SA, 2010-2012

	Model 1: Full Sample			Model 2: Females Only			Model 3: Males Only		
Variables:	**OR†**	**95% CI**		**OR†**	**95% CI**		**OR†**	**95% CI**	
Male Gender	2.42	1.51	3.88	-	-	-	-	-	-
Age - adjusted 5 year age groups	0.83	0.72	0.94	0.77	0.65	0.91	0.82	0.66	1.03
Duration of Treatment:									
<=0.83 years	3.83	2.06	7.13	4.13	1.82	9.40	5.38	1.84	15.72
0.83 - 2.05 years	1.33	0.71	2.50	2.00	0.90	4.47	0.99	0.33	2.96
2.05 - 3.58 years	0.91	0.47	1.76	1.44	0.62	3.33	0.63	0.21	1.88
3.58+ years	ref			ref			ref		
Reports any depressive symptoms in K-10 Questionnaire	2.21	1.35	3.61	2.42	1.23	4.77	2.40	1.13	5.11
No faith or not active in their faith (vs. somewhat or very active)	1.60	1.02	2.50	1.75	1.00	3.06	…	…	…
In the last 6 months, practiced safe sex often, sometimes, or never (vs. always)**	2.50	1.17	5.32	…	…	…	…	…	…
Has a partner or family member(s) that are HIV positive (partner/spouse, child, other)	1.70	1.03	2.82	…	…	…	2.44	1.01	5.90
Has a treatment supporter	2.02	1.13	3.64	2.49	1.19	5.20	…	…	…
Had a family member who died of HIV	…	…	…	…	…	…	2.98	1.29	6.91
Friend(s) knows they have HIV	2.02	1.23	3.33	…	…	…	3.67	1.46	9.23

*One person who was "worried" to go to clinic lumped in with "neutral"

**Excluding one person with missing data on practicing safe sex

"-" indicates not included in original model

"…" indicates included in original model but did not survive selection process

†Odds ratios were derived from logistic regression models

IRB Letter

TO: Vincent Marconi
Principal Investigator
MedInfect

DATE: February 28, 2012

RE: **Notification of Amendment Approval**
AM10_IRB00035109
IRB00035109
Risk Factors for Virologic Failure and HIV-1 Drug Resistance in Durban: A Case Control Study

Thank you for submitting an amendment request. The Emory IRB reviewed and approved this amendment under the expedited review process on **2/28/2012**. This amendment includes the following:

Personnel Change only: Adding Rachel Kearns as other Emory study staff.

In future correspondence with the IRB about this study, please include the IRB file ID, the name of the Principal Investigator and the study title. Thank you.

Sincerely,

Donna Thomas
Administrative Assistant
This letter has been digitally signed

CC	Patrick Sullivan	Ericka Tanisha	MedInfect MedInfect
	Del Rio	Carlos	Global Health

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