ABSTRACT

Objective: We sought to ascertain the individual-level factors associated with virologic failure (VF) in order to identify patients at risk for VF earlier in the course of antiretroviral therapy (ART).

Methods:   A case-control study of VF was conducted at McCord hospital in Durban. Cases were defined as patients with VF (viral load, VL > 1000 copies/mL) after > 5 months of first line ART and controls (2:1) were defined as patients with VL < 1000 copies/mL after > 5 months of first-line ART. Pharmacy refill frequency and pill counts were used as adherence measures. A semi-structured questionnaire including validated psychosocial and symptom measures was administered to all participants and additional data were collected from the medical record. Multivariate (MV) logistic regression models of VF included factors found to be associated with VF (p<0.05) in univariate analysis as well as age, gender, and ART regimen.

Results: A total of 158 cases and 300 controls were enrolled from October 2010 to June 2012. Median age was 38.4 years, 64.6% were women, median CD4 cell count 254 cells/uL and median VL 95,221 copies/mL for cases. In unadjusted analyses, adherence was significantly lower among cases than controls (p=0.0015). Adherence persisted as a significant predictor even after adjusting for age, gender, number of opportunistic infections, duration of ART, employment status, presence of support network, contraceptive use, and levels of fatigue, depression, and nervousness. All covariates were significant in unadjusted analyses but only age, gender, duration of ART, fatigue, and support network remained significant in the MV model. Nervousness was of borderline significance (p=0.086) in the MV model.

Conclusions: Pill counts combined with pharmacy refill data can provide a useful surrogate for VF serving as a potential ‘Early Warning Indicator’ in advance of routine VL monitoring. Adherence interventions may be targeted earlier for patients using this measure. Younger age, male gender, poor social support and stress-related symptoms are associated with VF independent of adherence metrics.

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INTRODUCTION:

As of 2007, nearly 33 million people were estimated to be living with HIV worldwide[[1](#_ENREF_1)]. Out of the 9.7 million people who were in need of antiretroviral therapy (ART), UNAIDS estimated that about 3 million people were receiving the life-saving treatment. Virologic failure (VF) is usually the earliest indication of ART uptake, adherence and clinical response in well-resourced settings. Those individuals with VF may indicate complete non-adherence to ART or can represent suboptimal adherence eventually resulting in HIV drug resistance (HIVDR) which can compromise future ART options. South Africa has been a model for efficiently rolling out ART for a large number of individuals with HIV. Many urban clinical programs within South Africa have reported low rates of VF despite a high volume of patients[[2](#_ENREF_2)]. However, as clinics in high-prevalence areas continue to scale-up ART delivery, a greater proportion of asymptomatic and underserved populations will inevitably challenge even the most effective programs to maintain low levels of VF.

The factors that contribute to VF are complex and interact at multiple levels[[3](#_ENREF_3), [4](#_ENREF_4)]. The World Health Organization (WHO) developed a set of early warning indicators (EWI) designed to identify programs and regions where HIVDR may be of great concern[[5](#_ENREF_5)]. These EWI include retention on first-line ART, on-time pill pickup and clinic appointment keeping, adherence as measured by pill count and viral load (VL) suppression 12 months after ART initiation. Several countries around the world are using EWI in order to focus efforts towards improving healthcare delivery in those settings with suboptimal scores[[5-7](#_ENREF_5)]. Although these “system-level” factors are useful at a programmatic and regional level, clinicians desire “individual-level” factors that could help identify and predict which patients may be at risk of VF while on ART or prior to initiation. While many studies have explored psychosocial, structural or clinical factors associated with adherence or VF, none have attempted a comprehensive assessment in this setting.

The Risk Factors for Virological Failure (RFVF) study was undertaken with the express intent of discovering “individual-level” risk factors that could predict or be associated with VF. We found several socioeconomic (structural), psychosocial and clinical determinants that could be employed in a real-world setting to assist programs in supporting those individuals with the greatest risk of VF and HIVDR. For programs that lack VL monitoring, these risk factors can also identify those individuals with VF and thereby assist clinicians in making changes to ART.

METHODS:

Clinical Setting:

The RFVF study was conducted at McCord Hospital (MCH) in Durban, South Africa, which is a regional referral center that has been treating patients with ART since 2002. MCH received partial support from the President’s Emergency Plan for AIDS Relief and South African government funding for ART which began in February 2004. Routine viral load (VL) monitoring occured 5 months after starting ART. If the VL was < 1000 copies/mL (cpm), patients were maintained on this regimen and followed with annual VL monitoring thereafter. If the VL was > 1000 cpm, a repeat VL was done 1-3 months later with concurrent adherence counseling. Pharmacy refills and pill counts were recorded for each patient in the clinic. If the VL remained > 1000 cpm, treatment changes were considered based upon the level of adherence and resistance testing.

Study Participants:

From October 2010 through June 2012, all individuals with HIV attending the MCH HIV clinic age 18 years or older who were receiving at least 5 months of their first ART regimen (substitutions allowed for toxicity) were offered participation in this study if they met the criteria for a case or control.

Study Design:

An unmatched case-control design was chosen for this study because the rate of VF was too low to justify a prospective cohort study and the intention was to allow for full investigation of all potential risk factors. Cases were defined as patients having a VL > 1000 cpm after > 5 months of their first ART regimen. Controls (2:1) were defined as patients with virologic suppression (VL < 1000 cpm) on > 5 months of their first ART regimen. In general, cases were identified as having VF within 1-2 weeks of a visit to the clinic (which corresponded to a pharmacy refill claim). These patients were notified and enrolled into the study if they agreed to participate within 1-2 weeks from that date. Their enrollment date was therefore 2-3 weeks from the most recent claim. Controls were randomly selected patients in the clinic who met the eligibility criteria and agreed to participate. Their date of enrollment corresponded to a claim date.

Data Collection:

All participants who provided consent and were enrolled into the study underwent a single, semi-structured interview in their preferred language with the research coordinator who was blinded to the study assignment. This interview consisted of a questionnaire, a validated neurocognitive assessment[[8](#_ENREF_8)], and a pill count. The questionnaire consisted of demographic, socioeconomic (including a wealth index, employment, education and cohabitants), psychological (including substance abuse, food insecurity, traditional African medicine use, safe sex practices, faith, stigma and intimate partner violence[[9](#_ENREF_9)]) and clinic satisfaction indices. There were also specific questions about ART adherence and clinic attendance based upon a modified ACTG adherence questionnaire. A study physician also met with each patient to review their medical history as well as to administer the Kessler 10 (K-10) depression scale, symptom screen and Karnofsky score. Clinical, pharmacy and laboratory data were also abstracted from the electronic and paper medical records. The study physician and medical record data were entered onto a case report form (CRF). Further details of the data collected can be found in Supplemental Table 1. Study data were collected and managed using REDCap electronic data capture tools hosted at Emory University.[[10](#_ENREF_10)]

Statistical Analysis:

The primary outcome assessed in this study was the dichotomized participant assignment as a case or a control. Separate sensitivity analyses used a VL threshold of > 50 cpm. All variables from the questionnaire and CRF were independently analyzed for their association with the primary outcome in univariate analyses. The “Access” variable represents ARV refill dates using the medication possession ratio (MPR)[[11](#_ENREF_11)] accounting for all refills occurring in the 180 days following the earliest refill date until enrollment. The Adherence variable utilized the enrolment date pill count and incorporated the dispensed pills over the previous 180 days[[12](#_ENREF_12), [13](#_ENREF_13)]. Although all variables were examined, only significant and epidemiologically important factors were presented. Individual analyses by domain were undertaken to identify appropriate variable categories, correlations and interactions between variables and ascertain which variables have the highest likelihood of success in multivariable models. Several multivariable models were constructed using model selection to arrive at each final model. Model 1 (baseline factors) attempted to identify the factors present at the initiation of ART most associated with the primary outcome. Model 2 included all time-updated variables except for the Access or Adherence measures. Model 3 included those socioeconomic and psychosocial variables from Model 2 that were likely to be correlated with the Access measure. Model 4 included those psychosocial, symptom, and clinical variables from Model 2 that were likely to be correlated with the Adherence measure. Model 5 was considered the full model including all time-updated variables and the Access and Adherence measures. Receiver operator characteristic (ROC) curves were constructed for each model.Subgroup analyses were performed to assess variables associated with VF among those individuals having only 12 months of first-line ART. Separate analyses were also performed which excluded the first 47 participants (25 cases and 22 controls) enrolled into the study as the clinical laboratory VL assay performed for MCH had identified a quality complication during the period of their enrollment.

Ethics:

The RFVF study was approved by the respective ethics committees at McCord Hospital and by the institutional review board at Emory University in Atlanta, Georgia.

RESULTS:

*Cohort description*

Overall, the mean age at enrollment was 39.6 (9.0) years and 64.6% were women (Table 1). The mean years of education was 10.5 for the cohort. Over 78% received an income and 19.0% were unemployed. There were 13.1% of individuals who used a personal vehicle for transportation to the clinic and 19.0% relied on family or a spouse to pay for ARVs and clinic visits. The majority of participants reported belonging to a religious faith (88.4%) but only 51.7% of participants were active in the expression of their faith. Traditional medicine was reportedly used in 57.6% of participants at some point in the past. Sixty-five percent reported having a current partner and 41.5% reported disclosing their status to a partner. Of the participants, 91.3% report having practiced safe sex always in the past 6 months (60.6% via condoms), and 42.1% had at least one family member living with HIV. Only 15.1% had an ART supporter and 80.1% were pleased with their clinic experience. The mean K-10 score was 12.8 (3.4) with 55.0% scoring >12. The most commonly reported symptoms were depression (34.5%), a rash (32.5%), and fatigue (32.1%). Nearly half (43.9%) felt their symptoms were related to ARVs. Only 34.7% of participants had no obvious neurocognitive impairment while 35.4% had evidence of HIV-associated dementia. Lipodystrophy was documented in 29.5% of participants. The median[Q1-Q3] CD4 count was 300.5 cell/µL (183.5-448.0) and tuberculosis was the most frequent opportunistic infection (54.8%). The mean duration of ART was 30.2 months (24.3). Most participants were encouraged to seek ART by either a doctor or nurse (43.4%). The vast majority of participants used their mobile phone to remind them to take ARVs or visit the clinic. The median[Q1-Q3] MPR was 1.03 (0.96-1.07) and median[Q1-Q3] pill count adherence ratio was 1.12 (1.05-1.17). Cases and controls differed substantially across all of the domains examined using univariate comparisons.

*Baseline risk factors (Model 1)*

Younger age and male gender were associated with VF in nearly all MV models (Table 2). Additional risk factors which were likely present at ART initiation included having a treatment supporter (OR 1.991), not having or not being active with a religious faith (1.634), having at least one family member living with HIV (1.613), having had a family member recommend the individual to seek ART, use of stavudine (d4T) in the current ART regimen, and use of fluconazole (4.973). The ROC area under the curve (AUC) was 0.7824 (Figure 1A).

*Overall risk factors excluding Access or Adherence measures (Model 2)*

In a full MV model that included all domains except the Access and Adherence variables, the factors that were associated with VF at the time of study enrollment included less than always practicing safe sex (5.500), not being pleased with their clinic experience (2.232), K-10 score >12 (3.136), symptoms of fatigue (2.532) and diarrhea (2.555), the absence of lipodystrophy (2.366), having lower recent CD4 counts (12.658), having a family member recommend the individual to seek ART, and having used a TV or radio as a reminder to take their ARVs (3.519). The ROC AUC was 0.8867 (Figure 1B).

*Access-related risk factors (Model 3)*

In a MV model that included the Access measure, the following remained significant after adjusting for the Access variable: practiced unsafe sex (3.108), K-10 >12 (3.064), and not being pleased with their clinic experience (2.584). The ROC AUC was 0.7952 (Figure 1C).

*Adherence-related risk factors (Model 4)*

Factors known to influence Adherence that remained significant after adjusting for the Adherence variable included not having or not being active with a religious faith (1.854), not being pleased with their clinic experience (1.934), practiced unsafe sex (5.905), K-10 >12 (2.689), symptoms of fatigue (2.471) or rash (2.011), low recent CD4 count (12.821), family member recommended the patient to seek ART, the use of d4T in the current regimen and used a TV/radio as a reminder for ARVs (3.363). The Adherence measure was also significant (1.328). The ROC AUC was 0.8851 (Figure 1D).

*Overall risk factors including Access and Adherence measures (Model 5)*

After adjusting for both the Access and Adherence variables, the following remained associated with VF: practiced unsafe sex (5.023), having at least one family member living with HIV (2.000), not being pleased with their clinic experience (1.965), K-10 >12 (3.021), symptoms of fatigue (2.470) or rash (1.992), low recent CD4 count (12.821), family member recommended the patient to seek ART, and used a TV/radio as a reminder for ARVs (3.681). Again, Adherence was significant (1.311). The ROC AUC was 0.8881.

*Sensitivity and subgroup analyses*

The following sensitivity and subgroup analyses (data not shown) are described in terms of how they differed from the whole cohort analyses. When the outcome was changed to a VL threshold of > 50 cpm, there were 265 controls and 193 cases (35 participants, 7.64%, were reclassified). Only six participants had a VL between 200 and 1,000 cpm. For model 1, ART duration and ethambutol (ETB) use were significantly associated with VF. Models 2 and 3 did not differ from the whole cohort models respectively. In model 4, diarrhea, the current ART regimen and fluconazole use were significantly associated with VF whereas Adherence was not significant. Age, diarrhea, fluconazole use were significant whereas Adherence was not. When only participants with 12 months of ART were included in the analyses, model 1 was largely unchanged. For model 2, being recommended by a family member to receive HIV treatment, the absence of lipodystrophy, and symptoms of fatigue and diarrhea were no longer significantly associated with VF. In model 3, being employed was associated with VF. In model 4, the first clinic for ART and the current regimen were associated with VF whereas fatigue and family recommendation for ART were not. Finally in model 5, fatigue and family recommendation for ART were not associated with VF. When the analyses were restricted to participants with a verified accurate VL, very few changes to each model were seen.

DISCUSSION:

The RFVF study sought to define the individual-level determinants for VF which could be used in this setting to identify patients at risk and what their specific barriers are prior to ART initiation and while on treatment (Table 3). This would enable targeted approaches for adherence interventions and could serve as surrogate measures for VF in settings where VL monitoring is not available. Most of the determinants we found were consistent across a large number of models and subgroup analyses. Key demographic, socioeconomic, psychosocial and clinical elements were associated with VF.

Within the Demographic domain, younger age was a predictor of VF at baseline and had a trend towards associating with VF when examining all variables but was not independent of Access and Adherence. Poor adherence and higher rates of VF for younger individuals has been described in many different settings[[14-20](#_ENREF_14)]. Additionally, male gender was associated with VF at baseline and in all other models confirming findings from previous studies. Not always dependent on adherence, these studies have shown men have poor health-seeking behaviors, higher baseline VL, lower ARV concentrations, and late presentation with advanced disease although women tend to have more ARV-related adverse events[[21-25](#_ENREF_21)]. From the Socioeconomic domain, relying on your own vehicle for transportation to clinic had a trend towards an association with VF and appeared to be independent of the Access variable which was unexpected. It is likely that this variable is highly correlated with another significant factor such as male gender.

From the Psychosocial domain there were several key variables identified. Symptoms consistent with depression and fatigue as well as practicing unsafe sex were markedly associated with VF in all models where those variables were examined independent of Access and Adherence. Depression has been linked to poor adherence but is also associated with other factors that could be independently associated with VF such as alcohol abuse which was infrequent in this study[[26-28](#_ENREF_26)]. Unsafe sex is likely marker for behaviors leading to VF. Safe sex may be a predictor of risky behavior, not following rules, superinfection, STI’s all of which may cause either poor adherence or an increase in VL[[29](#_ENREF_29)]. Not being active with a religious faith and having at least one family member with HIV were associated with VF in all models but was not highly significant. Religious faith has been shown to improve adherence but some studies have shown that certain practices could encourage prayer in lieu of ART[[30-32](#_ENREF_30)]. Although having a family member with HIV could promote mutual support, if the family member is ill, time, attention and ARVs may be diverted away from the participant and to that family member[[33](#_ENREF_33)]. Individuals who were pleased with their clinic experience were more likely to be controls in all models as has been shown in other studies that described the influence of the healthcare environment on clinic attendance and adherence[[34-38](#_ENREF_34)].

Several Clinical factors were associated with VF. Low CD4 count was highly associated with VF in all models and independent of Access or Adherence, confirming findings from previous studies[[39](#_ENREF_39)]. Also the use of d4T was associated with VF at baseline when compared to TDF (most commonly used), ZDV, ABC and ddI. The ART regimen only had a trend towards significant when more variables were included in the model. TDF-containing regimens have been shown to be better tolerated, more effective and have fewer side effects than d4T-containing ART[[40](#_ENREF_40)]. If a family member recommended the individual for ART, they were more likely to be a case in all models and independent of Access or Adherence. It is not entirely clear how family member referral could impact treatment outcomes. It is possible that family-driven stigma could be playing a role but it is more likely that this represents a lack of connection to primary care services or access to ART such as is common for men in this setting[[41](#_ENREF_41)]. Finally use of a television or radio to remind individuals to take their ARVs was suboptimal compared to using a mobile phone. Mobile phone reminders have been shown in clinical trials to promote adherence when weekly text messaging, daily calls or alarms are used[[42-44](#_ENREF_42)].

Poor Access as measured by the MPR was significant in a UV comparison but was not significant in any of the MV models. The MPR does identify major interruptions in ART which is ideal for NNRTI-based therapy but does not necessarily represent the proportion of days covered which is a more accurate measure of adherence. Suboptimal Adherence as measured by pill count was significantly associated with VF in all models where it was examined. Access and Adherence measures were highly correlated, ρ=0.68(p<0.0001) (Supplemental Figure 1).

When a lower VL (50 cpm) was used as the cutoff for cases and controls, only 35 participants were reclassified indicating that the lower threshold identified only a small percentage of additional cases. A recent modeling study showed greater cost-effectiveness when using the higher VL threshold in this setting[[45](#_ENREF_45)]. Using the lower cutoff, diarrhea and fluconazole use were associated with VF. While diarrhea could lead to diminished absorption, fluconazole increases ARV concentrations. Although this could lead to increased side effects and reduced ARV adherence, this seems less plausible. When restricting the analyses to individuals with only 12 months of ART, fatigue and family members recommending ART were no longer associated with VF.

Ultimately these factors interact in highly complex ways in determining an individual’s virologic response to ART (Figure 2). Pill adherence is a necessary final step required for VL suppression (assuming optimal pharmacokinetics) and can be a reasonable surrogate for actual pills ingested although pill dumping has been described in this setting. Access to clinic refills as measured by the MPR is not always a reliable indicator of adherence as it is not necessarily indicating ingested pills and individuals can obtain ARVs through other unmeasured sources. Although structural barriers have been well-described as leading to treatment interruptions, missed visits and poor adherence[[46-48](#_ENREF_46)], in our study, these factors appear to be secondary to psychosocial and clinical factors reinforcing the importance of a comprehensive approach to assessing determinants of health. Structural barriers can often be more readily addressed with discrete interventions (transportation and food assistance or improving the clinic environment) whereas psychosocial barriers can be more challenging to address.

There were several limitations to the current study. The RFVF study used a case-control design and as such, many of the variables obtained from the questionnaire relied upon a participant’s recollection of events that had occurred over the past 6 months. Although most cases were told of their virologic status within a week or two of their interview, this could have impacted some of the responses about overall wellbeing. Only one clinical site was examined which does not permit comparisons across diverse programs or geographic settings (rural or peri-urban).

In summary, the RFVF study provided real-world indicators for VF which could be used to identify patients at risk at the start of ART and while receiving ART. This would enable programs to tailor specific interventions for individuals with the intention to reduce the likelihood of VF and HIVDR. Furthermore, these determinants could be used in settings that do not have VL monitoring to assist clinicians in making decisions about switching ART. It is important to validate this questionnaire in other urban as well as rural settings. Eventually a more refined questionnaire could be tested prospectively.

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TABLES

**Table 1.** Selected cohort characteristics for cases and controls

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Domain/Characteristic | Overall  n=458 | Control  n=300 | Case  n=158 | p value |
| Demographic  Age at enrollment (mean)  Gender (%female)  Ethnicity (%black) | 39.6  64.6  98.9 | 40.9  71.0  98.7 | 37.1  52.5  99.4 | <0.0001  0.0001  0.66 |
| Socioeconomic  Education (mean years)  Income (%yes)  Employment (%UE)  Housing (%rent/own)  Transportation (%personal vehicle)  Wealth Index 1 (mean)  Wealth Index 2 (mean)  Payer source for ARVs (%family/spouse) | 10.5  78.6  19.0  50.2  13.1  0.0  0.0  19.0 | 10.2  82.0  16.0  52.7  9.7  -0.1  0.1  15.7 | 11.0  72.2  24.7  45.6  19.6  0.3  -0.2  25.3 | 0.0093  0.017  0.033  0.17  0.0035  0.83  0.053  0.017 |
| Psychosocial  Religious Faith (%yes)  Religion (%Christian)  Religious activity (%no religion/not active)  TM (%ever took)  Have a current partner (%yes)  Disclosed HIV status to partner (%yes)  Practiced safe sex in past 6 months (%always)  Safe sex practice (%used condoms)  Family Member HIV status (%positive)  Have an ART supporter (%yes)  Perceived stigma at clinic/hospital (%never)  Clinic experience (%pleased)  Traditional K-10 score (mean)  Traditional K-10 score (%12+)  Tired question from K-10 (%yes) | 88.4  97.0  48.3  57.6  65.1  41.5  91.3  60.6  42.1  15.1  99.8  80.1  12.8  55.0  44.3 | 91.3  97.8  41.7  58.3  60.7  38.3  95.0  56.0  38.0  11.3  100  88.0  12.3  48.3  39.7 | 82.9  95.4  60.8  56.3  73.4  47.5  84.2  69.4  50.0  22.2  99.4  65.2  13.7  67.7  53.2 | 0.009  0.069  0.0001  0.69  0.0073  0.072  0.0002  0.0064  0.017  0.0036  0.35  <0.0001  <0.0001  <0.0001  0.0075 |
| Symptoms and Exam  Fever, chills or sweats (%no)  Fatigue (%no)  Memory difficulty (%no)  Nausea or vomiting (%no)  Diarrhea (%no)  Felt sad or depressed (%no)  Felt nervous or anxious (%no)  Rash (%no)  Headache (%no)  Gastrointestinal intolerance (%no)  Sexual dysfunction (%no)  Weight loss or wasting (%no)  Hair loss (%no)  Pain or numbness of extremities (%no)  Any symptom felt related to ARVs (%yes)  Karnofsky score (mean)  Neurocognitive assessment  None  ANI/MND  HAD | 80.6  67.9  80.1  91.5  88.4  65.5  77.3  67.5  71.8  78.2  78.6  83.8  93.4  72.5  43.9  97.0  34.7  29.9  35.4 | 83.7  76.0  84.3  94.3  91.7  71.3  82.0  74.7  75.7  81.0  83.7  86.7  95.3  72.7  39.0  97.7  35.3  30.0  34.7 | 74.7  52.5  72.2  86.1  82.3  54.4  68.4  53.8  64.6  72.8  69.0  78.5  89.9  72.2  52.6  95.7  33.5  29.7  36.7 | 0.025  <0.0001  0.0029  0.0043  0.0052  0.0004  0.0014  <0.0001  0.016  0.057  0.0005  0.032  0.029  0.91  0.0078  0.026  0.89 |
| Medical History and Laboratory Values  Tuberculosis (%yes)  Cryptococcal meningitis (%yes)  Toxoplasmosis (%yes)  Lipodystrophy (%yes)  Renal dysfunction (%yes)  Recent CD4 count (median)  Recent CD4 count (%>350 cells/µL) | 54.8  1.7  1.1  29.5  2.4  300.5  41.9 | 54.7  1.7  0.7  37.0  2.0  359.0  52.0 | 55.1  1.9  1.9  15.2  3.2  206.0  22.8 | 1.00  1.00  0.35  <0.0001  0.52  <0.0001  <0.0001 |
| Medications  Mean ART Duration (months)  Initiating ARV Clinic (%Sinikithemba)  Recommended ART  Doctor or nurse  Family  Friend  Other  Current ART regimen contains  Stavudine (d4T)  Zidovudine (ZDV)  Other (tenofovir, didanosine, abacavir)  HIV education and training sessions (%3+)  Adherence counseling sessions  0 or 1 session  2, 3 or 4 sessions  5+ sessions  Mechanism to remember to take ARVs  Mobile phone (%yes)  TV or radio (%yes)  Clock or watch alarm (%yes)  Other (%yes)  Fluconazole use in the past 6 months (%yes)  TS use in the past 6 months (%yes)  INH or RIF use in the past 6 months (%yes)  ETB use in the past 6 months (%yes) | 30.2  90.0  43.4  23.4  14.4  18.8  21.0  21.4  57.6  95.2  10.1  70.9  19.0  88.9  8.3  11.1  6.3  3.7  51.3  13.5  2.8 | 33.0  92.7  42.7  19.3  16.7  21.3  17.3  24.7  58.0  97.3  6.0  78.0  16.0  91.0  5.3  10.3  4.7  1.0  44.7  9.3  1.3 | 24.7  84.8  44.9  31.0  10.1  13.9  27.8  15.2  57.0  91.1  17.8  57.3  24.8  84.8  13.9  12.7  9.5  8.9  63.9  21.5  5.7 | <0.0001  0.013  0.0068  0.0077  0.0050  <0.0001  0.060  0.0022  0.44  0.067  <0.0001  0.0001  0.0005  0.014 |
| Access MPR  Median  > Median (%)  > 90%(%)  > 80%(%)  > 70%(%) | 1.03  64.8  87.3  95.9  97.6 | 1.03  62.7  89.3  96.7  99.0 | 1.00  69.0  83.5  94.3  94.9 | 0.83  0.18  0.10  0.23  0.010 |
| Adherence Pill Count Ratio  Median  Highest Quartile (%)  Upper Middle Quartile (%)  Lower Middle Quartile (%)  Lowest Quartile (%)  > 90%(%)  > 80%(%)  > 70%(%) | 1.12  22.5  25.5  22.1  29.9  90.2  92.4  93.4 | 1.13  28.7  25.3  22.7  23.3  92.7  94.7  96.0 | 1.08  10.8  25.9  20.9  42.4  85.4  88.0  88.6 | <0.0001  <0.0001  0.020  0.015  0.0045 |

UE = Unemployed (seeking work or not seeking work), ARVs = antiretrovirals, K-10 = Kessler 10 depression scale, TM = any form of traditional (African, Chinese, Indian) or alternative/complimentary medicine, ANI = asymptomatic neurocognitive impairment, MND = mild neurocognitive disorder, HAD = HIV-associated dementia, ART = ARV treatment, TS = Trimethroprim-sulfamethoxazole, INH = isoniazid, RIF = rifampicin, ETB = ethambutol, MPR = medication possession ratio

**Table 2.** Multivariable analyses of risk factors for virologic failure using logistic regression

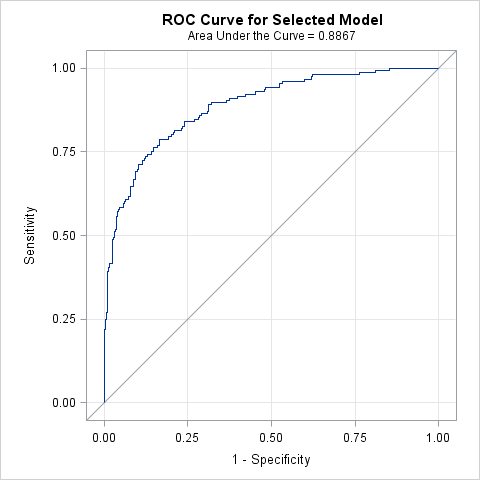
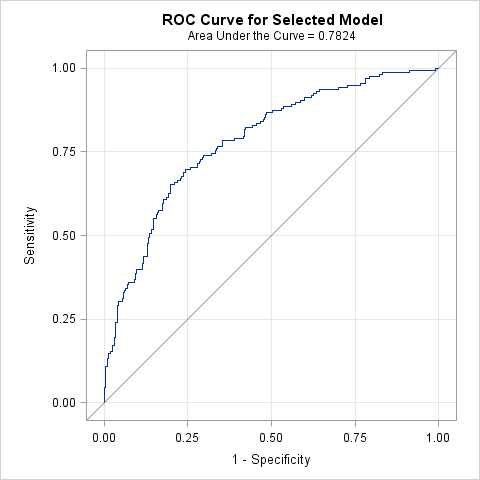
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Domain/Risk Factor | Model 1 | Model 2 | Model 3‡ | Model 4 | Model 5 |
| Demographic  Age (per 5 year increase)  Gender (male) | 0.956\*\*  1.995\*\* | 0.837†  2.262\*\* | 0.865†  2.524\*\*\* | 0.807\*  2.682\*\* | 0.860  2.416\*\* |
| Socioeconomic  Education (per 1 year)  Transportation (personal)  Pay for care (family/spouse) | 1.771†  1.517 | 1.112  1.789 | 1.111  1.979†  1.631 | --- | 1.108  2.034 |
| Psychosocial  Faith activity (none)  Practice safe sex (<always)  Family HIV+ (none)  Treatment supporter (yes)  Clinic feel pleased (yes)  Depression (12+) | 1.634\*  ---  0.620\*  1.991\*  ---  --- | 1.722†  5.500\*\*\*  0.593†  1.910  0.448\*  3.136\*\*\* | 1.533†  3.108\*\*  0.665†  1.807†  0.387\*\*\*  3.064\*\*\* | 1.854\*  5.905\*\*\*  0.588†  1.699  0.517\*  2.689\*\* | 1.802\*  5.023\*\*  0.500\*  1.783  0.509\*  3.021\*\* |
| Symptoms and Exam  Fatigue  Diarrhea  Sadness  Skin lesions | --- | 2.532\*\*  2.555\*  1.720† | --- | 2.471\*\*  2.026  1.401  2.011\* | 2.470\*\*  2.079  1.409  1.992\* |
| Medical History  Lipodystrophy (yes)  Log CD4 (per 1.0 increase) | ---  --- | 0.428\*  0.079\*\*\* | --- | 0.611  0.078\*\*\* | 0.608  0.078\*\*\* |
| Medications  ARV duration (per 1 month)  Recommend HIV clinic  Friend vs Family  Other vs Family  Provider vs Family  First Clinic (SKT)  ARV training sessions (3+)  Adherence counselling  2-4 vs 0-1  5+ vs 0-1  Current Regimen  ZDV vs d4T  Other vs d4T  Recall ARVs (TV/radio)  Trimethoprim/Sulfa (yes)  Fluconazole (yes)  Ethambutol (yes) | 0.995  0.424\*  0.446\*  0.879\*  0.503†  0.350†  ---  0.619\*  0.489\*  ---  1.625†  4.973\*  2.729 | 1.001  0.311\*  0.376\*  0.760\*  0.440†  0.370  0.416  0.649†  0.455†  3.519\*\*  0.624  2.636  2.800 | --- | 1.007  0.279\*  0.350\*  0.806\*  0.487  0.383  0.470  0.699  0.484  3.363\*  3.606 | 1.008  0.266\*  0.397\*  0.855\*  0.378  0.419  0.691†  0.435†  3.681\*\*  3.006  3.025 |
| Access (0.1) | --- | --- | 0.962 | --- |  |
| Adherence (0.1) | --- | --- | --- | 0.753\* | 0.763\* |

Odds ratios presented; †p value <0.10, \*p value <0.05, \*\*p value <0.01, \*\*\*p value <0.001, ‡Adjusted for ARV duration which was significant, Model 1 – baseline variables (excluding any time updated variables), Model 2 – full model without access or adherence variables, Model 3 – socioeconomic and psychosocial adjusted for access (forced), Model 4 – psychosocial, symptoms, clinical events and meds adjusted for adherence, Model 5 – full model with Access and Adherence forced; ARV – antiretroviral; --- variable or domain was excluded a priori

**Table 3.** Proposed questions.

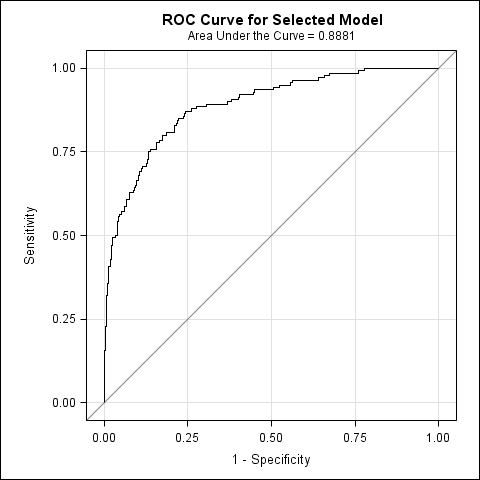
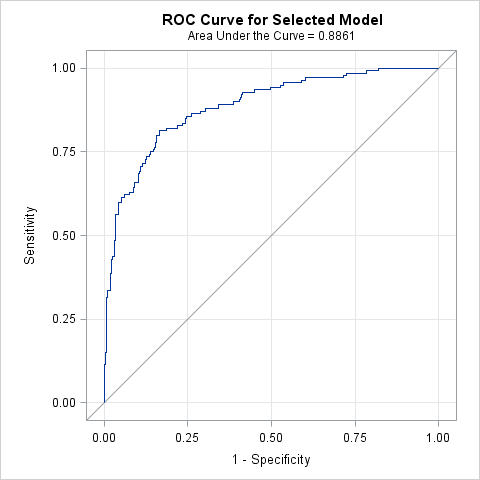
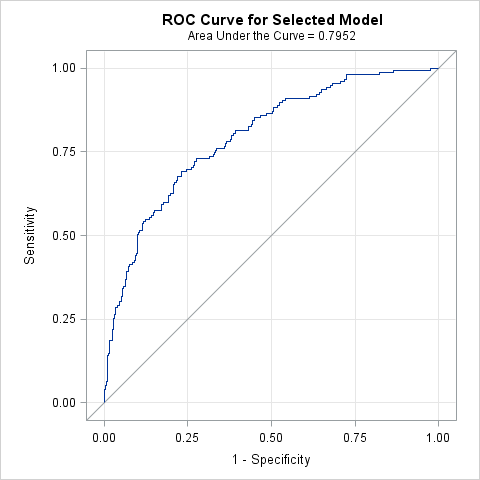
|  |  |  |
| --- | --- | --- |
| Baseline (While Initiating or Suppressed on ART) | On ART Without Access/Adherence Measures\* | On ART With Access/Adherence Measures\* |
| *Age*  *Gender*  *Faith*  *Family Member HIV+*  *Treatment Supporter*  *Clinic Recommendation*  *Current Regimen*  *Fluconazole Use* | *Depression*  *Unsafe sex practices*  *Clinic Experience*  *Fatigue*  *Diarrhea*  *Lipodystrophy*  *Current CD4 count*  *ARV Reminders* | *Depression*  *Unsafe sex practices*  *Clinic Experience*  *Fatigue*  *Rash*  *Current CD4 count*  *ARV Reminders*  *Adherence* |

\*These factors do not include those that were identified as baseline risk factors.



B.

A.



E.

D.

C.

**Figure 1.** Receiver operator characteristic curves for multivariable models 1-5 (A-E).



Institutional, Community and Societal Factors

Access

VL

Adherence

Socioeconomics

Comorbid Illness

Psychosocial

Medications

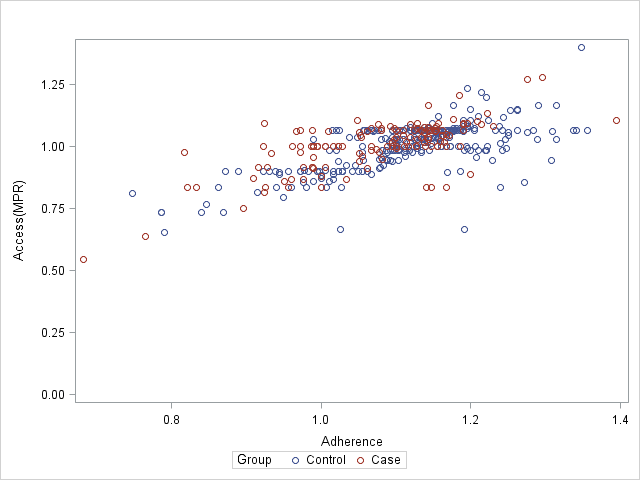
**Figure 2.** Schema of social, behavioural and clinical factors related to virologic response for individuals receiving antiretroviral therapy (ART). Pill adherence is necessary for viral load (VL) suppression; however, access to ART is neither necessary nor sufficient. Individuals can obtain ART from family or friends and may not swallow pills despite obtaining them. Socioeconomic factors (i.e. transportation to clinic) and comorbid illnesses have a more direct effect on ART access. Likewise, concomitant medications and psychosocial factors (i.e. stigma, disclosure, and depression) are more directly associated with ART adherence but also impact ART access. Institutional (healthcare, religious, governmental), community (neighborhood, dyadic) and societal (cultural, infrastructure, policy) factors have more global impact at all lower levels in this paradigm.

SUPPLEMENTAL MATERIAL

**Supplemental Table 1.** Quantitative measures that were adapted or modified to accommodate the local cultural and language context and needs of the study.

|  |  |  |
| --- | --- | --- |
| Domain | Measure | References |
| Demographic | Age, gender, race/ethnicity, education level, sensory impairment assessment | ACTG Adherence |
| Socioeconomic | Income, Employment status, Occupation, Housing, Transportation to clinic, Payer source for healthcare  Assets  Food Insecurity[[49](#_ENREF_49), [50](#_ENREF_50)] | ACTG Adherence  Wealth Index[[51](#_ENREF_51), [52](#_ENREF_52)]  Modified HFIAS index[[53](#_ENREF_53)] |
| Psychosocial | Marital status, Family and Partner information, HIV disclosure, Safe sex assessment, Religious faith assessment, Traditional and Alternative health practice assessment  Substance Abuse assessment  Intimate Partner Violence assessment,  Depression scale  Clinic satisfaction survey  Stigma assessment[[54](#_ENREF_54)] | ACTG Adherence and CAGE[[55](#_ENREF_55)]  DHS Domestic Violence Module[[9](#_ENREF_9)]  Kessler 10[[56](#_ENREF_56)]  Dahab et al.[[57](#_ENREF_57)] |
| Symptoms and Exam | Symptom assessment  Functional status  Neurocognitive Testing | ACTG Adherence  Karnofsky Performance Status[[58](#_ENREF_58)]  Digit Span Forward/Backward, Trail-Making Test A/B[[8](#_ENREF_8)] |
| Medical History | AIDS-defining conditions[[2](#_ENREF_2)], serious non-AIDS-defining conditions, HIV-1 RNA viral loads, CD4 T cell counts | Not applicable |
| Medications | ARV regimens (current and previous), ART initiation site and referral, ART education, Adherence sessions, Self-reported Adherence questionnaire, ART refill and ARV reminders, concomitant medications | ACTG Adherence |
| Access | Pharmacy refill dates and dispensed amounts over the preceding 180 days | MPR[[11](#_ENREF_11)] |
| Adherence | Pill counts at enrolment visit | Pill Count Adherence[[12](#_ENREF_12), [13](#_ENREF_13)] |

ART – Antiretroviral Therapy, ARV – Antiretroviral, ACTG – AIDS Clinical Trials Group; HFIAS – Household Food Insecurity Assessment Scale; MPR – Medication Possession Ratio, DHS – Demographic and Health Survey



**Supplemental Figure 1.** Correlation between Access and Adherence variables.