ABSTRACT

Objective: We sought to ascertain the individual-level factors associated with virologic failure (VF) and HIV-1 drug resistance (DR) in order to identify patients at risk for VF earlier in the course of ART and DR for patients with VF in the absence of DR testing.

Design: Case-control study.

Methods:   An ethics-approved 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:

Conclusions:

Word count: xx

**Title: Risk factors for virologic failure and HIV-1 drug resistance for patients on first line antiretroviral treatment (ART) in Durban, South Africa**

Running Headline: Virologic failure and drug resistance risk factors

Total words: xx (max yy)

Authors:

Vincent C. Marconi

Emory University School of Medicine, Atlanta, Georgia

Rollins School of Public Health, Emory University, Atlanta, Georgia

Atlanta Veterans Affairs Medical Center, Atlanta, Georgia

[corresponding author email: vcmarco@emory.edu and current address:

341 Ponce de Leon Avenue, Atlanta, GA, 30308, USA]

[Study design, Manuscript preparation and data collection]

Brent Johnson

Rollins School of Public Health, Emory University, Atlanta, Georgia

[Statistical analysis]

Jane Hampton

McCord Hospital, Durban, South Africa

[Study design and implementation, Data collection]

Baohua Wu

Rollins School of Public Health, Emory University, Atlanta, Georgia

[Statistical analysis]

Claudia Ordonez

McCord Hospital, Durban, South Africa

[Study design and implementation and critical review of manuscript]

Michelle Gordon

Nelson Mandela School of Medicine, Durban, South Africa

[Drug resistance testing and study design]

Anna Hare

Emory University School of Medicine, Atlanta, Georgia

[Statistical analysis]

Rachel Kearns

Rollins School of Public Health, Emory University, Atlanta, Georgia

[Statistical analysis]

Peng Wu

Rollins School of Public Health, Emory University, Atlanta, Georgia

[Statistical analysis]

Richard Murphy

[Critical Review of manuscript]

Jean Nachega

[Critical Review of manuscript]

Carlos del Rio

Rollins School of Public Health, Emory University, Atlanta, Georgia

[Critical Review of manuscript]

Daniel R. Kuritzkes1

Section of Retroviral Therapeutics, Brigham and Women’s Hospital, Boston, MA

[Study design and critical review of manuscript]

Henry Sunpath

McCord Hospital, Durban, South Africa

[Study design and implementation, Manuscript preparation and data collection]

SARCS Team Group Authors [Contributed to initial study design, Manuscript preparation and data collection]

[Helga Holst, Sally John, Roma Maharaj, Phacia Ngubane, Melisha Pertab, Sifiso Shange, Dinesh Singh (McCord Hospital, Sinikithemba Clinic, Durban, South Africa)]

Potential conflicts of interest

1. D.R.K. is a consultant to, or has received research funding from Abbott, Boehringer-

Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck and Roche.

**Key words:** first-line antiretroviral therapy, virologic failure, HIV-1 drug resistance, risk factors, South Africa, subtype C virus.

INTRODUCTION:

As of 2007, nearly 33 million people were estimated to be living with HIV worldwide. Out of the 9.7 million people who were in need of ART, UNAIDS estimated that about 3 million people were receiving the life-saving treatment. Virologic failure (VF)

METHODS:

Clinical Setting:

The Risk Factors for Virological Failure (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 counselling. 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 at least 5 months of their first ART regimen. Controls (2:1) were defined as patients with virologic suppression (VL < 1000 cpm) on at least 5 months of their first ART regimen.

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 neurocognitive assessment, 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) and clinic satisfaction indices. There were also specific questions about ART adherence and clinic attendance (access) based upon the modified ACTG adherence questionnaire. The research coordinator also conducted a validated neurocognitive assessment of the participant. A study physician also met with each patient to review their medical history as well as to administer a depression survey (based upon the Kessler 10), 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).

Statistical Analysis:

The primary outcome assessed in this study was the dichotomized participant assignment as a case or a control. Separate sensitivity analyses also used additional VL thresholds to include below the level of assay quantification and less than 200 cpm. All variables from the questionnaire and CRF were independently analysed for their association with the primary outcome in univariate analyses. 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. 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 objective measurements of access to care and ART adherence. Model 3 included those socioeconomic and psychosocial variables from Model 2 that were likely to be correlated with objective measures of access. Access was measured by xx. ART adherence was measured by xx. Model 4 included those psychosocial, symptom, and clinical variables from Model 2 that were likely to be correlated with objective measures of ART adherence. ART adherence was measured by xx. Model 5 was considered the full model including all time-updated variables and objective measures of adherence and access.Subgroup analyses were performed to assess variables associated with age and gender and those having only 6 months of first-line ART. Separate analyses were also performed which excluded the first 20 participants as the clinical laboratory testing VL for MCH had identified a quality complication during the period of their enrollment.

**Propensity score/AIC** – identify the markers to be used by clinicians

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:

DISCUSSION:

Acknowledgements

We would like to express our deepest admiration and appreciation for the patients who participated in the study and the work of the Sinikithemba Clinic at McCord Hospital in Durban, South Africa. The support for clinical research to improve patient care on the part of the counselors, medical records staff, nurses, and medical officers has been essential. Kristy Nixon provided vital assistance in the data collection. A special thanks to Daniel and Alessandra Marconi for forbearance.

Financial support

Grant support from Emory University Center for AIDS Research (CFAR) (P30 AI050409) and the Emory School of Medicine Division of Infectious Diseases, NIH (P30 AI60354 to Harvard University CFAR and K24 RR16482 to D.R.K.), Harvard University Program on AIDS, CDC Cooperative Agreement (U62/CCU123541-01), Elizabeth Glaser Pediatric AIDS Foundation as part of Project HEART, and the Gilead Foundation.

REFERENCES

TABLES

Table 1. Cohort Characteristics for case/control

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Characteristic | Overall | Control | Case | p value |
| Demographic  Age at Enrollment  Gender  Ethnicity |  |  |  |  |
| Socioeconomic  Income  Employment  ART Payer  Cohabitants  Education  Wealth  Transportation |  |  |  |  |
| Psychosocial  Depression old  Depression new  Faith  Religion(Local )  TAM  Stigma  Partner status  Partner #  Disclosure status  Safe Sex  Condom  ART Supporter  Clinic Feel |  |  |  |  |
| Symptoms and Exam  Fever  Fatigue  Memory  Nausea  Diarrhea  Sad  Nervous  Rash  Headache  GI upset  Sex problems  Weight Change  Hair loss  Pain  Related to ARVs  Karnofsky  Neurocognitive |  |  |  |  |
| Medical History  Recent CD4 Count  Tuberculosis  Cryptococcal meningitis  Toxoplasmosis  Lipodystrophy  Renal |  |  |  |  |
| Medications  Duration ART  Initiating ARV Clinic  Who recommended  Regimen  HIV Education  Adherence Counseling  Remember Meds  Fluconazole  Bactrim  INH  ETB |  |  |  |  |
| Access |  |  |  |  |
| Adherence |  |  |  |  |

Table 2. Multivariable Analysis for case/control

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Risk Factor | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 |
| Demographic |  |  |  |  |  |
| Socioeconomic |  |  |  | --- |  |
| Psychosocial | \* |  |  |  |  |
| Symptoms and Exam | \* |  | --- |  |  |
| Medical History | ---\* |  | --- |  |  |
| Medications | ---\* |  | --- |  |  |
| Access | --- | --- |  | --- |  |
| Adherence | --- | --- | --- |  |  |

\*excluding any time updated variables, Model 1 – baseline variables, Model 2 – adjusted for xx, Model 3 – socioeconomic and psychosocial adjusted for access, Model 4 – psychosocial, symptoms, clinical events and meds adjusted for adherence, Model 5 – full model

Separate subanalyses

1. Outcome for VL <200
2. Outcome for VL < assay
3. Exclude first 20 participants
4. Stratify or segregate for age and gender (see algorithm)
5. First 6 months on treatment only