Evaluation of patients on HIV antiretroviral treatment
in a comprehensive care clinic in La Romana, Dominican Republic

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HYPOTHESIS:
This study is not hypothesis-driven. Rather, it is an exploratory analysis designed to offer insight into factors associated with the clinical course of HIV and the response to antiretroviral treatment at a clinic in La Romana, Dominican Republic. This descriptive study will provide a basis for generating hypotheses for future study.

STUDY OBJECTIVES:
-Primary: To characterize the virologic, immunologic and clinical course of HIV and AIDS in patients receiving treatment at a comprehensive care clinic in La Romana, DR.

-Secondary: To identify predictors of treatment outcomes, including virologic, immunologic, or clinical treatment failure, adherence, mortality and retention in care among this patient population.

STUDY DESCRIPTION:
1. Study Purpose, Background, and Rationale
The Caribbean is considered the second most affected geographical region in the world in terms of HIV prevalence, with the Dominican Republic (DR) and Haiti accounting for nearly three-quarters of HIV cases in this area. Currently there are an estimated 62,000 [52,000-71,000] individuals living with HIV in the DR, a prevalence of .8% among the adult population[1]. In addition, there are 2,700 [2,200-3,000] children (less than 15 years old) living with HIV in the country[2]. Conservative estimates suggest that there have been 35,000 deaths attributable to HIV/AIDS in the DR since the beginning of the epidemic in the 1980s to the present and that HIV/AIDS is currently the primary cause of mortality among Dominicans 25-44 years old[3]. The burden of this epidemic is differentially distributed geographically and among particular vulnerable groups, especially commercial sex workers (CSW), men who have sex with men and Dominican-Haitian residents living on *bateys* or sugar cane plantations[4]. Of patients living with HIV/AIDS, it is estimated that only 24% of adults and children with advanced HIV infection are receiving antiretroviral therapy(ART)[2].

At present, little data exists on the characteristics of the AIDS epidemic in the DR and even less is known regarding the disease course and response to treatment among individuals. Evaluations of disease outcomes in clinics providing HIV comprehensive care in the United States, sub-Saharan Africa and Haiti have been published, but few studies have explored outcomes of ART in resource-poor Spanish speaking countries, such as the DR. This deficiency in knowledge limits the ability of treatment programs to target the subgroups in the country that have the highest risk for infection and makes it difficult for health care workers to anticipate the types of interventions (lab testing, medications, support services, etc.) needed to care for these patients. Observational studies that use clinical measures and laboratory values as surrogates for disease progression can be used to identify trends in the disease course and predictors of treatment outcomes in order to enhance our understanding of HIV in this setting[5]. The results can be used to ensure that existing treatment programs are tailored to the needs of the country and that additional treatment efforts are targeted to the appropriate populations.

The Clínica de Familia MIR (CF-MIR) is a family AIDS clinic in La Romana, in the Southeastern region of the Dominican Republic, where HIV rates have traditionally been among the highest in the country[6]. Since 2004, when highly active antiretroviral therapy became available at no cost to people living with HIV/AIDS in the DR, the International Family AIDS Program at Columbia University Medical Center (CUMC) has collaborated with CF-MIR to provide free, comprehensive and HIV-specialized care. This clinic, the second largest in the country, takes a multidisciplinary approach to family-centered HIV care and has been looked to as a model for HIV care in the country[4]. It is distinctive in its capacity to offer care to large cohort of children and in its outreach efforts treat some of the country's most marginalized populations including CSW and people living in *bateys*. The clinic was one of the first sites in the country to begin treating patients with long-term antiretroviral therapy and today cares for approximately 1,100 adult patients and 115 pediatric patients receiving ART[7, 8].

Because of the size and diversity of its patient population, CF-MIR offers a unique opportunity to examine the HIV epidemic in the DR. The data collected from clinic records will contribute to the knowledge base of the HIV epidemic in the Dominican Republic and generate hypotheses for future study. By examining the clinical course and disease outcomes of patients being treated at this clinic, we will be able to improve the quality of care in our own CUMC-associated facilities and inform the expansion of treatment initiatives in the Dominican Republic and other underserved areas.

2. Study Design and Statistical Procedures

This study is a retrospective analysis of prospective, observational data. Data will be abstracted from a review of clinic records including paper charts, electronic medical records and a log of medication pick-ups from the pharmacy. The data to be extracted includes demographic data, patient history, physical exam and laboratory data as available in the existing records.

The data will be analyzed with regards to two distinct subgroups: pediatric patients (<18 years old when treatment was initiated) and adult patients. Evaluation of the charts of the entire pediatric patient population of the clinic (n = 115) will allow for a thorough descriptive analysis of this group of patients. For the adult analysis, data will be extracted from the charts of a group of patients who have failed their first ART treatment regimen in the past five years, and an equal number of patients who have not failed treatment will serve as controls, matched on age and sex. We will review the charts of approximately 400 patients. These patients will be identified by an initial screening of the charts as described below.

- Study endpoints

We will collect data on the following clinically-relevant endpoints:

1) Treatment failure defined based on virologic, immunologic or clinical endpoints

-virologic: failure to suppress HIV-1 RNA <50 copies/mL after 12 months of treatment or HIV RNA >500 copies/mL after previously confirmed suppression of viremia (to <50 copies/mL)

-immunologic: as defined by the WHO standards, CD4 count at 12 months that was below the pretreatment baseline value (defined in this study as the CD4 count closest to the start of treatment and within 90 days of initiating treatment) or a fall in CD4 count to less than 50% of the maximum CD4 cell count while on therapy. A CD4 count of less than 100 cells/µL will be a definite failure and a count greater than 200 cells/µL will never be considered a failure[9].

-clinical: as defined by the WHO, occurrence of a new opportunistic infection or malignancy signifying clinical disease, recurrence of previous opportunistic infection,

onset or recurrence of WHO stage II conditions (including but not restricted to HIV wasting, chronic diarrhea of unknown etiology, recurrent invasive bacterial infections or recurrent/persistent mucosal candidiasis)[9].

2) Mortality
3) Loss to follow-up

- Sample size

At a maximum, the charts of 115 pediatric patients and 400 adult patients will be reviewed. This is an exploratory analysis, and sample size is determined by the number of children in treatment and adults with failure of their first-line regimen.

-Example minimum effect size analysis for predictors of treatment failure in pediatric patients

Case definition: patients with treatment failure defined as composite of virologic, immunologic or clinical treatment failure

Minimum effect size: (α = .05, 1-β = .80, assume normal distribution)

Baseline characteristics (at start of HAART)	**Estimated standard deviation**	**Group 2/Group 1: 9 (failure rate: 1/10, ~10 patients)**	**Group 2/Group 1: 4 (failure rate: 1/5, ~20 patients)**	**Group 2/Group 1: 1 (failure rate: 1/2, ~50 patients)**
Age (yrs)	6	5.7	4.2	3.4
CD4 (cells/uL)	100	94	71	57
Z scores (standardized weight for height)	25	24	18	14
Hemoglobin (g)	1.3	1.2	.92	.74
Ethnicity (proportion Hatian)	Estimated proporiton = .5	--	RR: 5 or 1/5	RR: 2 or ½

- **Analysis plan**

If deemed appropriate once the data have been collected and described, univariate analysis will be used to assess the impact of specific factors such as adherence, HIV risk factors, weight for age, age at treatment initiation, distance from clinic, etc. on pre-specified outcomes including treatment failure, mortality and loss to follow-up. If possible, factors significant in the univariate analysis, potential confounders and variables found significant in other models will be used to construct a multivariate logistic regression model to predict treatment failure.

3. Study Procedures

-Screening [Adult patients only, all children initiating ART in the last 5 years will be included in the study]
The charts of adult patients in the clinic will be screened to identify patients as treatment failures or patients who were lost to follow-up and corresponding controls. The information will be extracted and collected on a screening tool. The resulting database will contain the patients' clinic MRN number and the patients' de-identified study number. This database will therefore be kept separately and password protected. After it has been used to identify which charts will be used in the study, it will serve as a reference between patient charts and their study identifier in the event that their chart needs to be revisited for additional information. This form will be destroyed at the completion of the data analysis for this study.

-Data to be Collected

Data will be collected from available sources in the clinic only, including an electronic medical record, a paper chart and pharmacy refill data.

Demographic Data: Sex, age, ethnicity, marital status, living situation, employment status, HIV risk factors, living location (city/town only)

Patient History: approximate date of HIV diagnosis and initiation of ART, history of opportunistic infections (OIs), prior and current ART regimen, prior treatment for prevention of mother to child transmission, adherence to medication (as determined from clinic notes and pharmacy logs)

Physical Exam: Height, weight, BMI, evidence of OIs

Laboratory/Radiographic Data: CBC, viral load, CD4 count, evidence of OIs

This data will be recorded in a spreadsheet without any protected health information on the data extraction tool.

4. Study Drugs or Devices
No experimental drugs or devices will be used in this study.

5. Study Questionnaires
No questionnaires will be used in this study. The screening tool and data extraction tool that will be used to identify relevant charts are attached.

6. Study Subjects
- **Inclusion criteria**
Patients of all ages who have or are currently receiving antiretroviral therapy at Clinica de Familia MIR for treatment of HIV/AIDS since 2004.

- Exclusion criteria
Patients who have never received ART for the treatment of HIV will not be included in the study.

7. Recruitment
There will be no recruitment of patients for this study as it is retrospective in design.

8. Confidentiality of Study Data
Each patient will be given a unique identifier for research related to their clinical chart but kept confidential. The names and personal health information of the patients will never be disclosed. The birthdates of patients will be recorded in order to determine the age of initiation of ART and expunged once the age at ART initiation has been calculated. All patient charts will be maintained as per clinic protocol in a secure, locked location. All databases relevant to the study will be password protected, encrypted, and accessible only by study personnel.

9. Potential Risks
This study is strictly observational and does not involve any experimental treatments, procedures or protocols. There will be no difference in the treatment or level of care offered to patients enrolled in the study and patients not enrolled. As all data extracted will be purged of patient-specific identifiers and

protected health information, we do not anticipate the risk of loss of confidentiality.

10. Potential Benefits

There are no anticipated direct benefits to the patients enrolled in the study. Participants will receive neither financial incentives nor gifts of any significant monetary value.

11. Alternatives

There are no alternatives as this protocol is a retrospective chart review and will not directly impact individual participants.

STRENGTHS AND LIMITATIONS OF DESIGN

This study has the advantages of a typical chart review. It is an inexpensive means of accessing pre-existing data, it is easier to access conditions where there is a relatively long latency between exposure and disease (or start of treatment and outcome of interest), it allows for the study of relatively rare occurrences and it offers an opportunity for the generation of hypotheses that will be tested prospectively. This clinic, in particular, has the strength of a large and diverse population of patients undergoing treatment for HIV that will allow us to generalize about our conclusions.

The limitations of this study are largely that of incomplete documentation, including missing charts, information that is unrecorded, difficulty interpreting information found in the documents (jargon, acronyms, illegible writing), problematic verification of information and variance in the quality of information recorded by medical professionals. Data at the clinic is stored inconsistently between hand written charts and an electronic medical record. In addition, secondary to limited resources, some laboratory tests are preformed inconsistently. In particular, the measurement of viral load – considered the gold standard for definition treatment failure—is done infrequently, which is why we have to use the composite definition described above as our endpoint of interest. A case-control also does not allow for the establishment of causality between cause and effect.

NEXT STEPS

-Explore the relationship between treatment failure and loss to follow-up: determine most common causes for loss to follow-up; is there an association between treatment failure and loss to follow-up (are patients who are lost to follow-up more likely to fail treatment or are patients who fail treatment are more likely to stop receiving care) or is treatment failure and loss to follow up independent?

-Target patients who have failed treatment for enrollment in a cohort study designed to assess the impact of a structured adherence program on HIV outcomes.

-Design prospective studies and interventions based on predictors of treatment failure and loss to follow-up.

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