Interventions to Improve HIV Antiretroviral Therapy Adherence in Sofala, Mozambique

Pre-Analysis Plan

August 14, 2019

This document outlines the pre-analysis plan for the project "Interventions to improve HIV antiretroviral therapy adherence in Sofala province Mozambique." The primary objective of the study is to test whether financial incentives, phone-call reminders, information, and stigma-relieving interventions improve medication adherence of HIV-positive people starting antiretroviral therapy (ART). Participants were randomly assigned at the individual level to one of seven experimental groups:

1. Treatment Group 1 – receive *financial incentives* for refilling ART medications on time for six months;

2. Treatment Group 2 – receive *phone-call reminders* before ART medication refills for six months;

3. Treatment Group 3 – receive *phone-call reminders* before ART medication refills and *financial incentives* for on-time refills for six months;

4. Treatment Group 4 – receive the *information intervention*: upon recruitment, participants are shown a video about HIV progression, the mechanism of ART, benefits of adhering to ART;

5. Treatment Group 5 – receive the *anti-stigma intervention*: upon recruitment, participants are informed of the results of a recent population survey regarding people's attitudes towards HIV, if they overestimate the social stigma related to HIV;

6. Treatment Group 6 – receive both the *information intervention* and the *anti-stigma intervention*;

7. Control Group – no intervention.

Primary Outcome and Hypotheses

Our primary measure of adherence to ART is the *medication possession ratio (MPR) at least 95%, 6-month window*. This is an indicator variable that takes value 1 if MPR is greater than or equal to 95% and takes value 0 if otherwise. MPR is the proportion of days that a participant is in possession of at least one ART dose. MPR is computed from pharmacy dispensing records. The measurement window the 6-month follow up period. Measurement window will be truncated to the date that patients transfer clinics, opt out of future study participation, die, or lost to follow up.

We hypothesize that each treatment group will have higher values of the primary outcome variable, compared to the control group. To be explicit, we have one hypothesis for each of the treatment conditions:

1. Hypothesis 1: Participants who receive the financial incentive intervention alone will have better adherence to ART than the control group.

2. Hypothesis 2: Participants who receive the phone-call reminder intervention alone will have better adherence to ART than the control group.
3. Hypothesis 3: Participants who receive both the financial incentive and the phone-call reminder interventions will have better adherence to ART than the control group.
4. Hypothesis 4: Participants who receive the information intervention alone will have better adherence to ART than the control group.
5. Hypothesis 5: Participants who receive the anti-stigma intervention alone will have better adherence to ART than the control group.
6. Hypothesis 6: Participants who receive both the information intervention and the anti-stigma intervention will have better adherence to ART than the control group.

Primary Regression Specification

The following ordinary least squares regression will be used to test our primary hypotheses:

$$Y_i = \alpha + \beta_1 G_i^1 + \beta_2 G_i^2 + \beta_3 G_i^3 + \beta_4 G_i^4 + \beta_5 G_i^5 + \beta_6 G_i^6 + \boldsymbol{X}_i + \epsilon_i.$$

The regression is run at the individual level. Y_i is the outcome of interest for individual i. G_i^1, G_i^2, G_i^3, G_i^4, G_i^5 and G_i^6 are treatment group indicators, equal to one if individual i is in Treatment Group 1 to 6, respectively, and zero otherwise. $\boldsymbol{X}_i$ is a vector of control variables that includes:

- Indicator for female
- Years of education[1]
- Food security status[2]
- Time to travel to the clinic
- Knowledge about the risk of missing doses[3]
- Fixed effects for week of study enrollment
- Fixed effects for enumerator (baseline project staff) who enrolled the study participant at baseline

Tests of the statistical significance of coefficients β_1 through β_6 will be the basis for evaluating Hypotheses 1 through 6 for the primary outcome variable, as well as for the hypotheses associated with the secondary outcomes.

[1] Years of education takes integer values from 0 to 13, with 0 indicating illiterate, 1 to 12 indicating grade 1 to grade 12, respectively, and 13 indicating education level higher than 12th grade.

[2] Food security is an indicator variable equal to one if the participant answered "No" to both of the following questions, and equal to zero otherwise.

1. In the last 12 months, are there some days you go without food in your household?
2. In the last 12 months, did you or anyone else in your household ever cut the size of your meals or skip meals because there were not enough resources for food?

[3] Knowledge about the risk of missing doses is the number of statements of the following four that the participant correctly agreed or disagreed with (correct answer in parentheses below). It therefore takes on integer values between 0 and 4, inclusive.

1. Missing ART doses increases the risk of HIV transmission to others. (Agree)
2. Missing ART doses can cause HIV to develop resistance which would then lead to failure of the medication. (Agree)
3. Missing ART doses can increase the risk for me to become sick with AIDS. (Agree)
4. Even if I stop taking ART, my immune system will still function normally. (Disagree)

Secondary Outcomes and Hypotheses

We will also examine impacts of the treatments on the following secondary outcome variables. These secondary outcomes are simply different specifications or closely related outcomes to the primary outcome variable, so hypotheses for these secondary outcomes are analogous to those for the primary outcome: each treatment is hypothesized to improve ART adherence relative to the control group (coefficients β_1 through β_6 are expected to be positive).

- *Medication possession ratio (MPR) at least 95%, 3-month window*
  Definition analogous to that of the primary outcome of interest.
- *Medication possession ratio (MPR) at least 80%, 6-month window*
  Definition analogous to that of the primary outcome of interest.
- *Medication possession ratio (MPR) at least 80%, 3-month window*
  Definition analogous to that of the primary outcome of interest.
- *Medication possession ratio (MPR), 6-month window*
  MPR is the proportion of days that a participant is in possession of at least one ART dose (continuous variable between 0 and 1). The measurement window is the 6-month follow up period. Measurement window will be truncated to the date that patients transfer clinics, opt out of future study participation, die, or lost to follow up.
- *Medication possession ratio (MPR), 3-month window*
  Definition analogous to the secondary outcome immediately above, but for a 3-month follow up period.
- *Appointment attendance rate (AAR)*
  AAR is the proportion of scheduled visits completed during the observation period. "Completed visit" considered done if patient visits clinic on scheduled appointment date, or up to 7 days before that date. AAR is computed from clinic records. Measurement window truncated to last visit date for patients who transfer clinics, opt out of future study participation, or die.
- *Lost to follow-up (LTFU)*
  LTFU is an indicator variable. LTFU indicates patient missed the last appointment and 90 or more days have elapsed since the patient's last scheduled appointment date, with no clinic record of contact since that date. Patients who transfer clinics or opt out of future study participation are excluded from LTFU denominator, but those who die are retained in LTFU denominator. (Note this is a negative outcome, so reductions in LTFU indicate better ART adherence.)

We will also examine impacts of the treatments on the following additional secondary outcome variables. We hypothesize that Treatments 4, 5, and 6 (information, anti-stigma, and their combination) will have positive effects on each of these outcome variables, but that Treatments 1, 2, and 3 (incentives, reminders, and their combination) will have no effect on these outcome variables. In other words, coefficients β_4 through β_6 are expected to be positive, but coefficients β_1 through β_3 are expected to be zero.

- *Test Referral, 1-month window*
  This is an indicator variable, which takes value 1 if the participant makes a successful referral to test for HIV within 1 month of recruitment, and 0 otherwise. A participant is considered as having made a successful referral if someone approaches our study team in

the clinic, and presents us with the proof of an HIV testing together with the barcode card we distributed to the participant upon recruitment.

- *Change in knowledge about HIV and ART*
  Knowledge about HIV and ART is measured by the number of correct answers to five evaluating questions,[4] and so takes integer values from 0 to 5. The knowledge is measured in both the recruitment survey and the phone-call follow up survey one month after recruitment. The change in knowledge equals knowledge measured at the time of the phone call follow up minus knowledge measured at the time of the recruitment.
- *Change in belief about social stigma*
  Belief in social stigma is measured by answers to five questions.[5] Each answer takes value 0 to 10. The belief about social stigma is the sum of the five answers and it is measured in both the recruitment survey and the phone-call follow up. The change in belief about social stigma equals the belief measured at the time of phone-call follow up minus the belief measured at the time of recruitment.

In additional secondary analyses, we will examine the complementarity of the treatments that are offered alone or in combination. The test involves comparing the magnitude of the coefficient on the combined treatment with the sum of the coefficients on the component treatments alone. Specifically, we will examine whether the financial incentive and reminder treatments are complements (their impacts are greater than additive), substitutes (their impacts are less than additive), or neither (their impacts are exactly additive). We will do the same examining the interaction between the information and anti-stigma treatments.

Specifically, for Treatments 1, 2, and 3, the possibilities are:

- Complements: $\beta_3 > \beta_1 + \beta_2$
- Substitutes: $\beta_3 < \beta_1 + \beta_2$
- No interaction: $\beta_3 = \beta_1 + \beta_2$

[4] The five knowledge-measuring questions are as follows (correct answers in parentheses):

1. Can people get HIV from mosquito bites? (No)
2. Can people get HIV from kissing an infected person? (No)
3. Can HIV be transmitted from a mother to her baby during delivery? (Yes)
4. Can HIV be transmitted from a mother to her baby by breastfeeding? (Yes)
5. Do you agree with the following statement: Missing ART doses increases the risk of HIV transmission to others. (Yes)

[5] The five questions measuring belief about stigma are:
If, for each of the following questions, I ask 10 people living in the neighboring community, to each question, how many of the people I surveyed, do you think, will answer "Yes"? (Choose from 0, 1, 2, …, 10 for each questions)

1. Do you think that people living with HIV should always use separate dishware when sharing food with others to protect other's health? (stigmatizing guess = # of guessed "Yes")
2. Do you agree: I would be ashamed if someone in my family had HIV (stigmatizing guess = # of guessed "Yes")
3. If a female teacher has the AIDS virus but is not sick, should she be allowed to continue teaching in school? (stigmatizing guess = 10 - # of guessed "Yes")
4. Do you think that children living with HIV should be able to attend school with children who are HIV negative? (stigmatizing guess = 10 - # of guessed "Yes")
5. If a member of your family became sick with the AIDS virus, would you be willing to care for him or her in your household? (stigmatizing guess = 10 - # of guessed "Yes")

For Treatments 4, 5, and 6, the possibilities are:

- Complements: $\beta_6 > \beta_4 + \beta_5$
- Substitutes: $\beta_6 < \beta_4 + \beta_5$
- No interaction: $\beta_6 = \beta_4 + \beta_5$

Finally, we will conduct a secondary analysis that pools treatments to increase power to identify the effects of the incentive, reminder, information, and anti-stigma treatments. This will be done using the following regression specification that removes consideration of the effect of the combined treatments, and instead focus on indicators for receiving the treatment components, whether alone or in combination:

$$Y_i = \alpha + \gamma_1 Incent_i + \gamma_2 Remind_i + \gamma_3 Info_i + \gamma_4 Antistig_i + \boldsymbol{X}_i + \epsilon_i.$$

Compared to the primary regression specification, the indicator variables for each of six treatments are replaced by four indicators, as follows. $Incent_i$ is an indicator for receiving the incentive treatment, either alone (in Treatment 1) or in combination (in Treatment 3). $Remind_i$ is an indicator for receiving the reminder treatment, either alone (in Treatment 2) or in combination (in Treatment 3). $Info_i$ is an indicator for receiving the information treatment, either alone (in Treatment 4) or in combination (in Treatment 6). $Antistig_i$ is an indicator for receiving the anti-stigma treatment, either alone (in Treatment 5) or in combination (in Treatment 6). The regression specification is otherwise identical to the primary regression specification.

Subgroup Analysis

The primary regression analysis will be run in subgroups to assess heterogeneity of treatment effects. We will test for equality of the coefficients of interest within each pair of subgroups. The following subgroups will be examined:

- Male vs. female;
- Above median education (inclusive) vs. below median education;
- Food secure vs. food insecure;
- Above median time to travel to the clinic (inclusive) vs. Below-median time to travel to the clinic;
- Above median knowledge about the risk of missing doses (inclusive) vs. Below-median knowledge about the risk of missing doses;

We consider these subgroup analyses to be secondary analyses.

Corrections for Multiple Hypothesis Testing

For the primary analysis (impact on MPR 95%, 6-month window) we will use the List, Shaikh and Xu (2016) procedure to correct p-values to account for the presence of multiple treatment conditions.

All secondary analyses are considered exploratory, so we will conduct no multiple hypothesis corrections for secondary analyses.

References

List, John, Azeem M. Shaikh, and Yang Xu (2016). "Multiple Hypothesis Testing in Experimental Economics," NBER Working Paper 21875, January 2016.