HIV Development Assistance and Adult Mortality in Africa: A replication study of Bendavid et al. (2012)

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A replication study proposal submitted to 3ie's Replication Window 3: HIV Prevention (RW3)

Preliminary information

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Replicated Article:

Bendavid E, Holmes CB, Bhattacharya J, Miller G (2012). HIV Development Assistance and Adult Mortality in Africa, *JAMA* 307(19):2060-2067.

1. Introduction

Study Selection: To identify highly impactful studies in HIV prevention we considered the most recent 94 studies available in the 3ie Repository published between 2011-2014. We calculated the publication rate by using the number of citations for each study from the Web of Science database and months since publication. We weighted each publication rate with journal Impact Factor to identify the top 10 most impactful studies using these criteria:

Study for Replication: The study by Bendavid and colleagues, "HIV Development Assistance and Adult Mortality in Africa" published in *JAMA* in 2012, was ranked in the top five studies based on our impact score criteria. This study investigates the relationship between increased funding to countries receiving aid through the President's Emergency Plan for AIDS relief (PEPFAR) and adult mortality more generally. PEPFAR began its first full year of funding in 2003 and provides funding to 15 focus countries for delivery of antiretroviral therapy (ART) and other human immunodeficiency virus (HIV) prevention programs.[1] Funding allocated to PEPFAR countries has increased dramatically between 2004 and 2010,[2] but the effectiveness of the increased funding to focus countries on adult mortality had not been well studied. Previous studies addressing this question had either shown no effect of increased PEPFAR funding on adult mortality during a fairly circumscribed time frame (2000-2006)[3] or used estimates with modeled data of mortality rates.[4] Bendavid and colleagues sought to determine whether trends in mortality following PEPFAR funding reflect benefits beyond HIV-related mortality using a broader time frame since PEPFAR implementation as well as survey data of individuals to more directly measure mortality. The authors performed two main analyses: a cross-country comparison of adult mortality between 1998 and 2008 in 9 African countries receiving PEPFAR funding (focus countries) and 18 African countries that did not receive funding (non-focus countries), and a within country comparison of the intensity of PEPFAR implementation within 22 districts of Tanzania and 30 districts in Rwanda and adult mortality.

The main finding of the study was that adult mortality declined more dramatically (8.3 per 1000 in 2003 (95% CI, 8.0-8.6) vs 4.1 per 1000 in 2008 (95% CI, 3.6-4.6)) in countries receiving PEPFAR funding; however, they could not distinguish between effects on total adult mortality and effects solely on HIV-related mortality. Similarly, they could not detect a difference in adult mortality that was associated with PEPFAR implementation intensity between districts within Tanzania and Rwanda. Two other factors were associated with

lower adult mortality: the educational level of the women respondents to the individual household surveys and the effectiveness of the government.

The findings from the Bendavid and colleagues generated a substantial amount of debate. In a subsequent JAMA article, Shelton challenged the estimate of the association between mortality and PEPFAR funding,[5] suggesting that the estimates of reduction in mortality should have accounted for population size and the prevalence of HIV within each country. In the same issue, Emmanuel wrote an editorial piece about the implications of the Bandavid study for funding world health programs.[6] In 2014, Bendavid and Battacharya looked more broadly at health outcomes and funding for health aid, and found that life expectancy increased and mortality rate of children under five years of age decreased with investment.[7]

Since policy decisions often hinge on whether aid allocation has a significant and intended impact, understanding the relationships between these factors is of critical importance.[8]

2. Replication objectives and research questions

The first objective of the proposed replication is to conduct a pure re-analysis of the original study data. Specifically, we will regenerate all the published results according to the exact methods and data provided in the original paper and related appendix. The second objective is to compare the methods used in the original paper to the study conducted by Duber et al.[3] The third objective is to validate and generalize the statistical methods proposed in the original paper to additional data.

The following are the specific aims for this replication study:

Aim 1: Conduct a pure re-analysis of the original study data using the methods and data from the original paper.

We will follow the methods proposed in the appendix and define the related variables first, then reproduce all the results. We will assess any difference between our analyses and results from the original paper and appendix.

Aim 2: Compare the methods used by the original paper and that used by Duber et al.[3]

Since the results from Duber et al.[3] found no significant difference in 13 of 14 health indicators between PEPFAR focus and non-focus countries, we will directly compare the

statistical methods used by the original paper and that used by Duber et al.[3] In particular, we will carefully compare the methods in defining new variables and parameters from existing ones. But we will not replicate the study by Duber et al. and only compare the analysis methods and other differences, say data set, countries, and period.

Aim 3: Explore potential limitation to Duber's method.
We will assess the measurement, methods and procedures used in Duber's study as part of the proposal. Since the data included in Duber's paper are from countries in Africa, which often have similar economic, social and cultural conditions, the data from these countries may be correlated. Additionally, the mortality rates within focus and/or non-focus countries may vary and form some clusters. Both correlation and clustering can weaken the power for our hypothesis testing. We will conduct alternate analyses using Bendavid's method with Duber's data.

Aim 4: Generalize the methods used in the original paper.
We will test the generalizability of the methods used in the original paper by using updated data posted on WHO Statistical Information System (WHOSIS). These data are publicly available (http://www.who.int/whosis/data/Search.jsp) and allow us to test the updated data set using the same analysis plan.

In the above aims, we will further explore the applicability of all the results by Bendavid et al. (2012) and generate new findings based on the original analyses.

3. Replication plan and statistical methods

3.1 Pure replication

The study by Bendavid et al. measured the associations of PEPFAR with all-cause mortality via a logistic regression model. This replication will examine whether the findings are supported with re-analysis. We will identify all independent variables and response variables defined in the paper. Next, following the methods as described in the paper, we will examine the reproducibility of the analytical methods as well as any potential bias in the analytical procedures. The following are our detailed steps for the pure replication study.

1) Data management and preparation: Data will be prepared in a format that can be used for analyses. In the analyses of adult mortality, we will establish a longitudinal data set using person-level information from the Demographic and Health Surveys (DHS) following the methods proposed in the paper. We will start with the data and create Table 1, ”Study Countries, Participants, and Group Designation” for survey information in the original paper.

2) Logistic regression and logistic difference-in-difference analysis: After the preliminary data analysis described in Step 1, we will examine the association of PEPFAR and all-cause mortality between focus and non-focus countries. Since mortality is a binary variable, we will fit a logistic regression model, a common model for binary response data. Individual-level factors (such as sibling age in years, the index woman’s education, place of residence, etc.) and country-level factors (such as HIV prevalence, gross domestic product per capita, per capita development assistant for health from all sources other than PEPFAR, etc.) will be adjusted for in the analysis. Because this is a replication study, variables (such as indicator for focus countries, country-level covariates, covariates for person, mean mortality probability, etc.) included in the model will strictly follow the approach used in Bendavid et al.[10]. A table for mortality odds within Tanzania and Rwanda will be also generated from our analysis.

3) Estimation of Deaths Averted: Three steps will be used for estimating the number of all-cause adult deaths averted. First, the results from logistic regression described in Step 2 will be used for calculating the predicted probability of mortality for all individuals in the focus countries from 2004 through 2008 using the main adjusted regression coefficients for two scenarios: an “actual” scenario where PEPFAR is implemented and a “counterfactual” scenario where it is not implemented. Second, we will calculate the mortality benefit associated with PEPFAR as the mean of the difference between the two scenarios for each focus country from 2004 through 2008. Third, we will estimate the number of deaths averted by multiplying that difference by the size of the adult population (see Bendavid et al.[10]).

4) Cross-country analyses: We will compare population, HIV prevalence among adults, GDP per capita, etc. between focus and non-focus countries and will list corresponding p-values in Table 2, “Comparison of Focus Countries and Nonfocus Countries With Each Other and With Nonstudy Sub-Saharan Countries”, Table 3, “Regression Models

Estimating the Odds Ratio of Death in Study Adults in Focus Countries vs Nonfocus Countries" and the related supplementary tables will be replicated. We will also redraw Figure 1, "Trends in Development Assistance for Human Immunodeficiency Virus to Focus Countries and Nonfocus Countries: Mean per-Country Assistance in 2008 US Dollars, 1998-2008"; Figure 2, " Age-Adjusted Adult Mortality Trends in the Focus and Nonfocus Countries, 1998-2008" as well as eFigure 1, "Country-level annual adult mortality trends, 1998-2008". Here eFigures and eTables are the table in the supplemental material.

5) Sub-national analyses: eTable 1, "Baseline characteristics of administrative regions in Tanzania and Rwanda", eTable 2, "Odds ratios of mortality within Tanzania and Rwanda" in the appendix and Figure 3, "Adult Mortality trends in Tanzania Separted by PEPFAR Activity, 1998-2008" will be reproduced.

6) Spillover mortality effects: We will generate eTable 3, "Estimation of the number of deaths averted for the period 2004 to 2008".

7) Sensitivity analyses: We will follow the original paper and systematically leave one country and regenerate eTable 4, "Leave one country out analysis" and estimate the odds of death associated with PEPFAR for subsets of countries and surveys (eTable 5, "Relative odds of death associated with PEPFAR for subsets of countries and surveys"). We will also reproduce eTable 6, "Sensitivity Analysis Using Linear Time Trends".

3.2 Comparison

We will also compare the statistical analysis methods between Bendavid et al.[10] and Duber et al.[3] Since their conclusions concerning mortality are discordant, we will carefully compute variables involved in the statistical analysis using the raw data. Our focus will be on the variable definitions provided by Bendavid et al.[10] The data used by Dubar et al. from http://www.pepfar.gov and http://www.who.int/whosis/data/Search.jsp will be utilized for this analysis. We will apply the methods described in the Bendavid et al.[10] to this data set. We will be able to directly compare results from the two analyses of same data. Duber et al. used 46 countries in WHO African region and variables or health indicators were from years 2000 and 2006. But Bendavis eta al. used 27 countries from 2004 to 2008. Since health effects are an accumulating processing, their differences might be caused by different time periods used. Or the differences might be the country

coverage or analysis methods. This comparison will find the reason. The two data sets were collected in the same countries of Africa and are comparable. We will briefly discuss the impact of Duber et al. paper.

3.3 Validation and Limitation

After assessing the measurement, methods and procedures used in in Duber's and Bendavid's papers, we will study the possible limitations of Duber's paper. Since Duber's paper uses simple statistics to describe the health indicators without incorporating related factors that affecting health conditions, we would like to see how Bendavid's method might help us to overcome these issues. We will use Bendavid's methods on Duber's data and see if those alternative methods alter Duber's conclusions. Duber's data are available online (http://www.pepfar.gov and http://www.who.int/whosis/data/Search.jsp) via registration and submitting short proposal.

3.4 Generalization

We will utilize the methods in the original paper to analyze updated data posted on WHO Statistical Information System (WHOSIS). All these data are publicly available for us at hhp://www.who.int/whosis/data/Search.jsp so we can verify if the conclusions of Bendavid generalize to a bigger data set. WHOSIS contains more data and Duber data are parts of it. WHOSIS has almost all data collected by WHO in different years for different diseases and health indicators, but Duber data contain only years 2000 and 2006 for 46 African countries.

Through above analyses, we will further explore the applicability of all the results produced by Bendavid et al. (2012) and generate new findings based on the original analyses.

We will also study the association between Gini coefficient and HIV related markers[13] if related data are available. If macroeconomic data such as GDP, Gini coefficient etc are available and we have enough time to do so, We will study the robustness of the original paper using multi-level analysis[14, 15].

The modeling and analysis methods are as follows: Highest level, an indicator for PEPFAR focus and non-focus countries will be used, say 1 for focus and 0 for non-focus. GDP related variables, say GINI coefficient, will be country level factor since they are only defined for each country. Social-economic-status is a family-level variable. If we have family data and our interest is HIV infection incidence in a family (yes: 1; no: 0),

then we will incorporate GDP, PEPFAR focus or non-focus, and social-economic-status into a logistic regression with HIV infection as response variable. Usually this will be a mixed model since some variable may be random. For other aspects of multilevel models, please see Gelman and Hill.[15]

Tentative time frame

Months	Task
1-2	Preparation: Manage data and get ready for the analyses
3-5	Aim 1: Conduct pure replication, mainly program and regenerate all the tables and figures
6-7	Aim 2: Compare the methods between between Bendavid et al.[10] and Duber et al.[3]
8-9	Aim 3: Validate the analyses
10-11	Aim 4: modify computer program from Aim1 and analyze new data
12	Finishing: Prepare report and write manuscripts

4. Conclusions

Our goals in this replication study are to test the reproducibility of the results and conclusions in Bendavid et al.[10], compare the methods used in the original paper with Duber et al. [3], validate the model assumptions in the original paper, and generate new findings by applying the methods to new data. If the model assumptions in Bendavid et al.[10] are not satisfied, we will provide alternative methods.

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