# Effect of a Cash Transfer Programme for Schooling on Prevalence of HIV and Herpes Simplex Type 2 in Malawi, A Replication Study of Baird (2012)

Lynette M. Smith, Ph.D.

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

**Principle Investigator:**

Lynette M. Smith, Ph.D., Associate Director
Center for Collaboration on Research, Design and Analysis
College of Public Health
University of Nebraska Medical Center
984375 Nebraska Medical Center
Omaha, NE 68198-4375
lmsmith@unmc.edu

**Replicated Article**

Baird S, Garfein R, McIntosh C, and Ozler B. 2012 "Effect of a Cash Transfer Programme for Schooling on Prevalence of HIV and Herpes Simplex Type 2 in Malawi: A Cluster Randomized Trial". *The Lancet* 379: 1320-1329.

## Introduction

The study selected for replication is "Effect of a Cash Transfer Programme for Schooling on Prevalence of HIV and Herpes Simplex Type 2 in Malawi: A Cluster Randomized Trial" by Sarah Baird, Richard Garfein, Craig McIntosh,and Berk Ozler published in The Lancet 2012. This study uses a fairly new approach to address structural drivers of HIV/AIDS described as 'physical, social, cultural organizational, community, economic, legal or policy aspects of the environment that influence the risk and vulnerability environment and thus acting as barriers to, or facilitators of, HIV prevention and treatment behaviour' (Blankenship et al. 2000, Sumartojo et al. 2000). In the current study, monthly cash transfer (to influence an economic structural driver), that was not accompanied by a program or training directly related to HIV prevention, decreased both the prevalence of HIV and herpes simplex virus 2 (HSV-2) as well as the sexual behavior of the young women receiving transfers for 18 months.

The study included 1289 Malawian women (13-22 years of age) who had never been married and were enrolled in school at the beginning of the study. Participants either received cash monthly ($1-$5 monthly and their parents to receive $4-10 monthly) or received nothing. For the intervention group receiving cash, subjects were further required to attend school to receive payment or given no requirements for payment. After 18 months, HIV prevalence was reduced 64% and HVS-2 was reduced 76% with cash transfer, regardless of whether school attendance was required.

The impact of this study lies both in the study population considered and the *absence* of intentional HIV prevention training during the intervention. Young girls between the ages 15-24 represent 30% of new HIV infections in southern Africa (Deller et al. 2015), and while antiretroviral treatments have shown promise to prevent HIV acquisition, none of the trials to date have been tested in adolescents (Abdool Karim and Deller 2014). Other studies have improved economic empowerment of young women through microfinance loans (Hall et al., 2006, Pronyk, et al. 2008, Dunbar et al. 2010) or subsidies to pay for school uniforms or other education costs (Duflo et al. 2006), but typically only measure sexual behavior post-intervention or measured other STIs as a proxy for sexually risky behavior rather than HIV prevalence directly.

The current study measures prevalence of HIV and HVS-2 directly in participants at the end of the study. The results suggest that the structural intervention of cash transfer alone was enough to affect behavior. Specifically, young women in the intervention group were more likely to choose younger partners and report less frequent sex with those partners even though the study found no effect on the frequency of unprotected sex. Lucy Cluver et al (2013) found in an observational study in South African that receipt of a cash transfer was associated with reduced incidence and prevalence of transactional sex and age-disparate sex in girls aged 12-17,

which agrees with the current study. Hallfors and colleagues (2015) conducted a similar three-year intervention, but subsidized school costs specifically for 328 orphan adolescent girls. While other beneficial effects were found such as improved likelihood to stay in school, socioeconomic status and reduced likelihood to marry in the intervention group versus controls, there was no difference in HIV or HSV-2 prevalence after 5 years.

## Replication Plan:

**Pure replication:** We propose to first reproduce the results presented in the paper using the author's raw data and reported statistical methods as a pure replication. From the corresponding author's website, https://sites.google.com/site/decrgberkozler/papers-by-topic replication code is available and the authors own replication results are shown on the website. With the authors code the pure replication should go smoothly. During the pure replication we will replicate the results found in tables 2, 3, and 4. We will also confirm non-significant results mentioned in the text but not shown in the tables: "Analysis of secondary outcomes with the 12 month follow-up survey data, such as school enrolment, marriage and pregnancy, and sexual behaviour, showed no effects in this group of participants who did not receive cash transfer offers despite living in intervention enumeration areas (data not shown), and biological data were not collected from these study participants at the 18 month follow-up." As long as data is provided on the subjects that don't have biological data we will confirm the negative secondary outcome results.

Stata will be used for the pure replication which should match the original analysis exactly since that was the software used for the study. The analysis will also be done using the SAS survey procedures, which we would expect to show similar results (within rounding error) as found with Stata.

**Measurement and estimation analysis:** After the verification of the original analysis results, we will examine the robustness of the findings through additional analyses.

First, we consider the design strategy applied in the paper for recruiting patients is fairly convincing as well as the analysis presented in the paper. The original analysis calculated unadjusted and adjusted odds ratios by fitting logistic regression models. Robust standard errors were calculated allowing for intracluster correlation, and sampling weights were included to adjust for the probability of inclusion based on age and enumeration area stratum.

Alternative methods exist for estimation for this type of study design, including generalized linear mixed models or GLMM (also known as hierarchical or multilevel models). Sophia Rabe-Hesketh and Anders Skrondal

and Pfeffermann et al. describe a multilevel model for complex survey data. Their model can be implemented in Stata with the package gllamm or in SAS with PROC GLIMMIX. With the GLMM we can do an intent-to-treat analysis as in the original paper. This model allows for estimation of random effects as well as fixed effects. Random effects take into account the clustered nature of the data. We will use this model to look at outcome variables that were statistically significant or close to being statistically significant in the original paper, specifically: HIV and HSV-2 prevalence at 18 months, Enrolled in school during 2008, Sexual debut, Had unprotected sexual intercourse, Had sexual intercourse once per week, and Had a sexual partner aged >= 25 years. The fixed effects included in the adjusted models will be intervention status, age of the girl, geographical location (urban, rural and far rural), and if the outcome variable is measured at baseline it will also be included. Enumeration area will be included as a random effect. The baseline schoolgirls and baseline dropouts will be treated as two separate cohorts for analysis. A separate analysis for the baseline schoolgirls will be conducted with the intervention classified as conditional cash transfer, unconditional cash transfer, and control, as was done in the original paper.

From these models we can look at the amount of variability due to both the enumeration area and the individual. If the GLMM estimated odds ratios differ from those originally reported by more than 10% for the primary outcome variables (HIV and HSV-2) we will conclude that the results are somewhat sensitive to the model choice. This model also allows us to address some concerns that Webb et al. (2012) Lancet commentary makes regarding this article (http://www.sciencedirect.com/science/article/pii/S0140673612614421). They make an important point that cluster-level baseline characteristics are not reported in the paper. We will calculate and report the intercluster variability and other cluster level statistics including median and range for the number of subjects per cluster. From the GLMM analysis we can get a measure of the intraclass correlation between the enumeration areas, which wasn't reported in the original article and is recommended by the CONSORT guidelines.

In Webb et al.'s (2012) Lancet commentary, the authors stated that "the point estimate without clustering had a very wide confidence interval and was not significant and only after significant adjustment was there a significant findings." Since the design of the study incorporates multistage sampling and unequal sampling probabilities, the analysis must include those components to have unbiased results. Crude odds ratios that are not adjusted for the sampling design can be calculated based on the data provided, but will be biased. We will explore Webb's critique that the results are sensitive to the adjustment to weights and cluster size. Group permutation-based methods account for the cluster randomization and for the intraclass correlation of enumeration areas. These methods account for the dependent nature of outcomes among study participants in the same area. An advantage of group permutation testing is that no distributional or

modeling assumptions need to be specified. Note that Peterson et al (2002) did not use covariates in their primary analysis in order to maintain the model-free nature of randomization-based permutation methods.

In permutation testing, the enumeration area is considered to be the experimental unit (and thus accounts for the intraclass correlation within enumeration areas by permuting the areas) rather than individuals. The permutation test statistic used is the difference in overall average between the control and experimental groups, but others can be used as well (Peterson et al, 2000). Permutation tests were used by the well-known statistician Sir R.A. Fisher (Fisher, 1935). These methods can be used when asymptotic theory does not apply, for example with small sample sizes. The real advantage is that they require few distributional assumptions, as mentioned earlier. Although these methods may not be as powerful as parametric methods, there are instances where they have greater power (Anderson, 1999).

In general, hypothesis testing begins with the assumption that the null hypothesis of no treatment effect is true, and we examine the test statistic and derive the sampling distribution of the test statistic under the null hypothesis. For permutation tests, the procedure is essentially reversed. For permutation testing, the procedure is:

1. Define a test statistic that is large if the treatment effect is large and small if the treatment effect is small.
2. Define the null hypothesis.
3. Create a new data set consisting of your data, randomly rearranged (permutations).
4. Calculate the test statistic for the randomly arranged data set and compare it to the observed test statistic.
5. Repeat steps 3 and 4 several hundred times.
6. If the observed test statistic is greater than 95% of the randomly generated test statistics, then you can reject the null hypothesis at $p<0.05$.

The primary outcomes for this study include prevalence of HIV and HSV-2 at 18 months. Prevalence of syphilis is also calculated. It is possible that these binary outcomes are correlated with each other, though we may find they are not correlated. HIV prevalence rates can include girls who were perinatally infected which would not be associated with risky behaviors or HSV-2. We will attempt to model the interrelationship between the outcome, risk factors (including the intervention), and between the different outcomes. Bivariate outcomes examined will be HIV and HSV-2; included in the model as fixed effects are intervention, age of the girl, and geographical location (urban, rural and far rural), and random effect for enumeration area. Intervention will be examined in two ways, as was done in the original analysis, first as intervention vs. control and then split into three groups, conditional cash transfer, unconditional cash transfer and control. The baseline schoolgirls and baseline dropouts will be treated as two separate cohorts for analysis.

A multivariate approach will be applied, using generalized estimating equation (GEE) methodology to fit a simultaneous survey logistic regression to multiple binary outcomes, specifically HIV and HSV-2 (Lu and Yang 2012). This methodology allows for the complete modeling of the data in one analysis, testing correlations between multiple outcomes and directly estimating the difference in the association between risk factors and multiple outcomes. By employing a multivariate model, it is possible to gain precision compared to estimating separate models for each outcome. This could be an important advantage when event rates are small, such as in this study by gaining in terms of precision. This method could be of particular use for examining the difference in the rates of HIV/HSV-2 in the conditional vs. unconditional case transfer groups. The study was under-powered to detect difference between those groups and the bivariate model could increase the power for that comparison.

One advantage of the bivariate analysis is that allows for the simultaneous estimation of the treatment effect on outcome, enabling complete information from multiple outcomes in single analysis. Outcome specific effects and overall risk factor effect can be estimated simultaneously as well as examining the difference of the association between risk factors and multiple outcomes. This analysis method also permits the testing of correlations between multiple binary outcomes. These models can be fit using PROC GLIMMIX. One disadvantage to this type of model is that the models do not always converge. With binary outcomes this problem may be exacerbated. Various correlation structures can be attempted to overcome the convergence issues.

**Theory of Change Analysis:** The paper is modelling the outcome measured after intervention using cluster, weighted, logistic regression with adjustment of baseline measurements, we will extend the study by (1) directly evaluating the treatment effects on the outcome to evaluate the effects of the intervention on improving the HIV awareness (for example: having a HIV test, or gaining of HIV knowledge); (2) composing a wealth index of the participants using principle component analysis based on the available data and evaluate whether the wealth index at baseline (Filmer and Pritchett, 2001) will influence the effects of the intervention; and (3) modeling the causal pathway implied by the study.

1) A composite HIV awareness variable will be created, based on some of the survey variables including Had and HIV test, knows a healthy looking person can have HIV, knows that HIV can be transmitted through breastfeeding, and received health training about HIV/AIDS. A principle components model can be used to produce the composite HIV awareness variable. We will examine the treatment effect on this composite HIV variable using a survey linear regression model, adjusting for baseline levels of awareness, the subject's age, and geographic area (urban, rural and far rural).

2) A wealth index can be constructed using variables collected at baseline which are shown in table 2, and include mother alive, father alive, female headed household, household owns a radio, television, access to a mobile telephone, electricity and piped water available. From these variables a principle component analysis can be conducted to produce the wealth index such as described by Wamani et al. The wealth index variable will be included in a multiple logistic regression model, along with the intervention, and the interaction between the wealth index and the intervention variable, age of the girl and geographic area (taking into account the design of the study). Models for HIV and HSV-2 prevalence at 18 months will be run separately as well as separate models for baseline schoolgirls and baseline dropouts. One might expect that the cash transfer intervention would be most effective in poorer households. As Pettifor et al. points out "conditioning payments on school attendance may only be relevant in settings where there is a financial barrier to schooling". By looking for interactions with the wealth index, we can begin to determine if this type of intervention is unequally effective based on the wealth of the individual. This may be most interesting in the baseline dropouts cohort of the study. This group of subjects may be in most need of the cash transfers in order to attend school, and by definition is most at risk. With the wealth index we can determine if the effect of the intervention on outcome is affected by wealth, i.e. is there less of an effect in higher wealth groups and more of an effect in the lower wealth groups.

3) The causal pathway implied in the study is shown in Figure 1.

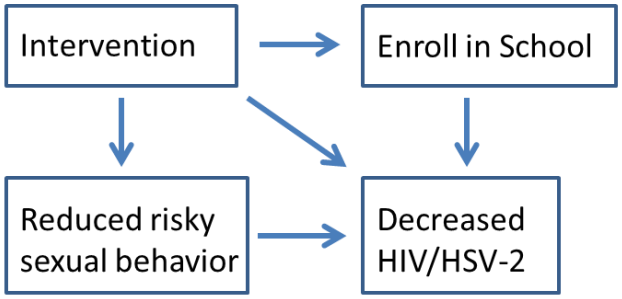
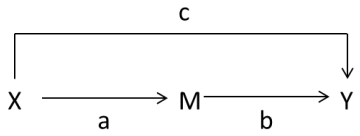



Figure 1. Pathway for reduced HIV/HSV-2 prevalence.

The authors of the paper examined the intervention in univariate and multivariate models on whether the participant Enrolled in School in 2008, on the prevalence of risky sexual behaviors, and on the prevalence of HIV and HSV-2 at 18 months. In the theory of change analysis, we will look at whether Enrolled in School and risky sexual behaviors (Sexual debut, Had unprotected sexual intercourse, Had sexual intercourse once per week, and Had a sexual partner aged >= 25 years) are directly related to HIV and HSV-2 prevalence at 18 months. The intervention of cash transfers lasted from baseline to 24 months, Enrolled in School in 2008 and the sexual behaviors are measured at 12 months during the course of the intervention, and

prevalence of HIV and HSV-2 are both measured at 18 months. Since Enrolled in School in 2008 and the sexual behaviors are measured prior to HIV and HSV-2 it should be valid to look at the association between these variables. Baird and colleagues have looked extensively at the connection between the intervention and school enrollment, but the direct connection between enrollment in school and risky behaviors and HIV/HSV-2 prevalence have not been assessed in this study. Another potential pathway would be intervention effects school enrollment which in turn effects risky behaviors and then HIV/HSV-2 prevalence, but is likely that they are all interconnected. Associations between Enrolled in School in 2008 and risky behaviors can also be examined, but the direction of the relationship cannot, since they were measured at the same time point. The model will employ the survey weights and clustering as in the logistic regression models described in the original paper, adjusting for baseline characteristics and geographical location.

We can explicitly investigate pathway specific effects to see how much of effects of the intervention are mediated through reduced sexual behavior and through enrollment in school. To do this we will use a four step approach proposed by Baron and Kenny (1986). This approach involves a series of 4 regression models shown pictorially below. X is the intervention variable, M is the mediator variable (school enrollment or risky sexual behaviors), Y is the outcome variable, a, b are direct effects and c is the direct effect of X on Y.




To test this, we run the following models:

| | Analysis |
|---|---|
| Step 1 | Predict Y with X to test for path c.<br>$E[Y]=B_0+B_1X$ |
| Step 2 | Test for path a, the effect of X on M.<br>$E[M]=B_0+BX$ |
| Step 3 | Test for path b, the effect of M on Y.<br>$E[Y]=B_0+B_1M$ |
| Step 4 | Multiple regression with X and M predicting Y.<br>$E[Y]=B_0+B_1X+B_2M$ |

If one or more of these relationships are not significant then we can conclude that mediation is not likely in this case. If relationships exist in steps 1-3, then we can look at step 4. If the effect for M in the multiple regression model is significant we can conclude there is some form of mediation, if X is not significant, then it is full mediation, if both are significant then the model supports partial mediation.

Table 1: Tentative time frame

| Months | Task |
|---|---|
| 1-3 | Communicate with the original authors to obtain the raw data and understand the data |
| 4-5 | Conduct the pure replication of the study |
| 6-7 | Conduct the measurement and estimation analysis: sensitivity analysis, and multivariate modeling of outcomes. |
| 8-11 | Conduct the theory of change analysis: modeling awareness, creating and modeling the wealth index, causal pathway modeling |
| 12 | Compare results, write report, and prepare manuscript |

**Personnel**

The research team for the project will include a biostatistics faculty member as the primary investigator, a biostatistics PhD student and a programmer. We have found that employing research teams for project enables timely completion of the projects.

PI

Dr. Lynette Smith has worked as a statistician in the Department of Biostatistics for 15 years. She has extensive consulting experience working as a collaborator and statistician on many projects ranging from lab based studies, clinical trials, epidemiology studies, and projects derived from national databases such as the HCUP NIS database, MEPS and NSQIP. Both the NIS and MEPS databases include a stratified sampling design and employ sampling weights. Ms. Smith has expertise in modeling procedures for different types of data including linear modeling, generalized linear modeling, and generalized linear mixed modeling for correlated data. Ms. Smith has over 150 publications from this collaborative work. Ms. Smith's dissertation work is on prediction methods for spatially correlated multivariate count

data. She will mentor the PhD student, manage, analyze, and interpret all quantitative data.

PhD student

A PhD student in the Department of Biostatistics will be a collaborator on this project. Funds from this project will be used to support a percentage of the Graduate Assistantship for one of the students. Currently, there are 4 PhD students in the Department and 4 additional students are expected to matriculate in Fall 2015. All students have a Master of Science in Biostatistics, Statistics or a related field. Thus, students come to the PhD program with knowledge of applied statistics as well as mathematical statistics. All students take a graduate level SAS course as part of their first semester of study since many master's programs do not provide formal SAS training. This course provides fundamentals in data management and analysis using SAS and prepared students for the Base SAS Certificate. Core courses for the PhD program include theory and modeling for linear models, survival models, generalized linear and mixed models. Advanced theoretical courses in probability and inference comprise the remainder of the core courses. Elective courses include applied modelling for categorical data, survival data, correlated data, clinical trials as well as a variety of epidemiology courses. All students will be paired with a faculty mentor with expertise relevant to the specific project.

Programmer

Mr. Eugene Boilesen will be the programmer for the project. Mr. Boilesen has extensive experience in data management and SAS programming. He will compile the data, create SAS permanent datasets, and manage the data.

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