Treatment as Prevention
A replication study on early antiretroviral therapy initiation and HIV-1 acquisition

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Abstract

Early antiretroviral treatment (ART) of an HIV-1-infected individual has been shown to lower the risk of transmitting HIV to his or her non-infected partner, as first shown in the study known as HPTN052 published by Cohen et al. (2011). It had been common practice to delay ART until one's CD4 count fell below a specified number of cells per cubic millimetre; however, based on the HPTN052 study and other studies World Health Organization (WHO) recommended that anyone infected with HIV-1 should begin ART as soon after diagnosis as possible. This paper conducts a pure replication study of HPTN052 by Cohen and colleagues. Using the data shared by the authors and applying methods described in the original paper, we were able to replicate most of the tables and the shape of the figures included in the original paper. We found a major difference in the number of participants used for creating the figures that displays the main results of the paper. We also found minor differences, mostly in table 2. The discrepancies between the replication and the original study found are due to the breakdown of hazard ratios (and associated confidence intervals) by periods of follow-up; while the total numbers are the same, the breakdown between year intervals differ. We note that these minor differences between our pure replication and the original paper results did not change the statistical significance of these findings, which were not statistically significant in the original paper for the most part. In conducting the time-to-event analysis, we find that the number of participants at risk of HIV-1 infection at year 0 since randomization was 1718, whereas this number was 1775 in the original paper. Even though this difference did not fundamentally change the nature of the graph of the Kaplan-Meier estimates (figure 3), the number of participants at risk at different years since the randomization in our pure replication is different from the numbers presented in the original paper. In this pure replication, we were able to reproduce the main result of the original paper. As in the original paper, our replication shows a relative reduction of 96% in the number of linked HIV-1 transmissions resulting from the early initiation of antiretroviral therapy, as compared with delayed therapy.

1. Introduction

Since September 2015, World Health Organization (WHO) has recommended that anyone infected with HIV should begin antiretroviral therapy (ART) as soon after diagnosis as possible. With its "treatment-as-prevention " recommendation, WHO removed all limitations on eligibility for ART among people living with HIV, all populations and age groups are now eligible for immediate treatment. Before, the recommendation by WHO was to initiate ART once an individual's CD4 cell count dropped below a certain level, sicker individuals having lower counts. The threshold CD4 count for ART initiation in lower-resource countries increased from 200 in 2006 to 350 in 2010, and to 500 in 2013. These changes were supported by the results of several randomized controlled trials that showed improved outcomes with earlier treatment (Severe et al. 2010; INSIGHT START Study Group, 2015; TEMPRANO ANRS Study Group, 2015).

At the same time, a study known as HPTN052 was undertaken by Cohen et al. (2011) which aimed to assess whether, in addition to benefitting the patient, HIV treatment could lower the risk of an HIV-infected individual transmitting HIV to his or her non-infected partner. Cohen et al. (2011) enrolled 1763 HIV serodiscordant (one partner is HIV-1-positive and the other is HIV-1-negative) couples at 13 sites in 9 countries (Gaborone, Botswana; Kisumu, Kenya; Lilongwe and Blantyre, Malawi; Johannesburg and Soweto, South Africa; Harare, Zimbabwe; Rio de Janeiro and Porto Alegre, Brazil; Pune and Chennai, India; Chiang Mai, Thailand; and Boston, USA). Enrollment took place from June 2007 through May 2010. Patients with HIV-1 infection were eligible if their CD4 count was between 350 and 550, they were in a stable sexual relationship with their partner and they had received no previous antiretroviral therapy except for short-term prevention of mother-to-child transmission of HIV-1. After the enrollment, HIV serodiscordant couples were randomly assigned in a 1:1 ratio to either receive ART immediately (early therapy, n=886), or after a decline in the CD4 count (two consecutive measurements of 250 or less) or the development of an illness related to acquired immunodeficiency syndrome (delayed therapy, n=877). The primary prevention endpoint was genetically linked HIV-1 transmission in HIV-1–negative partners. The primary clinical endpoint was the earliest occurrence of pulmonary tuberculosis, severe bacterial infection, a WHO stage 4 event, or death. Cohen et al. (2011) through an individual randomization trial determine the impact of early therapy on the primary prevention endpoint and the primary clinical endpoint.

The authors find that early initiation of ART reduced sexual transmission of HIV-1 among HIV-1 negative partners. Specifically, the authors find that 39 HIV-1 transmissions occurred since enrollment. Of these, 28 were biologically linked to the HIV positive partners. Of the 28 linked transmissions, only 1 occurred in the early therapy group. This difference represents a relative reduction of 96% due to the early initiation of antiretroviral therapy ($P<0.001$). Furthermore, the authors find that for serious HIV-1-related clinical events (i.e. a WHO stage 4 event, severe bacterial infection or pulmonary tuberculosis, or death), observed in HIV-1-infected participants, 40 were in the early-therapy group and 65 in the delayed-therapy group (hazard ratio, 0.59; 95% CI,0.40 to 0.88; $P= 0.01$). Finally, the authors find that 246 HIV-1– infected participants had one or more severe or life-threatening adverse events (grade 3 or 4) representing 14% in the early-therapy group and 14% in the delayed-therapy group ($P = 0.64$). The most frequently reported adverse events included infections, psychiatric and nervous system disorders, metabolism and nutrition disorders, and gastrointestinal disorders.

The study was halted prematurely due to overwhelming evidence that indicated that early ART was associated with a 96% lower risk of index-to-partner transmission. It was the first study to suggest that HIV treatment could prevent transmission and serve as a prevention method. Since carefully implemented clinical trials in a controlled research environment may not reflect what would happen in a real-world setting, several studies have been initiated to test the treatment as prevention approach at population level (Hayes et al. 2017; Iwuji et al. 2018; Gideon Amanyire et al. 2016;). As such, HPTN052 was a seminal study in suggesting treatment is prevention and was the basis on which additional studies were designed.

The influence of the HPTN052 study and the magnitude of effort required to scale up universal access to ART underscores the importance of carefully reviewing, understanding, and verifying the study

results. Therefore, in this paper we use the data from the original authors to replicate methods used and to produce the results presented in the original paper. In this paper, we present the pure replication as the first part of the replication of the study of Cohen et al. (2011). Specifically, we present the data used, the methods used by the original authors and used to conduct the pure replication, and the results of the pure replication.

2. The pure replication

In this section, we used the data provided by the original authors and methods described in the original paper to reproduce the results presented in the original paper. We first present the data received from the original authors, then the methods used to conduct the pure replication, and finally the results of the pure replication.

2.1 The data

The data used to conduct this replication was provided by the Cohen et al. (2011) in the end of 2018, after several requests dating back to 2015. We received four datasets from the original authors: *hivanadat_new.dta*, *index.dta, othanadat_new.dta,* and *partner.dta.* We constructed all variables required for the replication by using data obtained from the original authors using the methods specified in the original paper. The data provided by the original authors were obtained in SAS format and converted to Stata 15.1. We used Stata 15.1 to conduct the pure replication.

Index.dta contains the data used for data analysis of baseline characteristics of HIV-1 infected participants. It contains 1,763 individuals including demographic (age, sex, sexual activity, region, etc.) and clinical data (Plasma RNA viral load, type of serodiscordancy, etc.). We should note that *index.dta* contains two variables for sex: PMDsex and IDMsex, the latter of which reproduces the numbers in the original table for demographic information on sex. We used this dataset for the reproduction of the findings for HIV-1 infected participants in table 1.

Partner.dta contains similar baseline demographic data as *index.dta*, however for 1775 HIV-1 uninfected participants. *Partner.dta* obviously does not have clinical data, as these variables do not apply to individuals who are uninfected with HIV-1. However, we must note that *partner.dta* does not reproduce the original numbers for sex, we had to use *hivanadat_new* (described below) and the variable PMDsex to reproduce the variable for sex for HIV-uninfected participants. It is unclear in the materials provided by Cohen et al what the difference is between PMDsex and IDMsex. We used this dataset for the reproduction of the findings for HIV-1 uninfected participants in table 1.

othanadat_new.dta contains variables such as the site ID, ID, the randomization arm (treatment or control), biological sex, CD4 absolute, etc. for 1763 HIV-1 infected individuals. This dataset contains survival time data wherein the failure variables are those with "event" in the name, the duration variables are those with "dura" in the name, and the exit dates are those with "_dt" in the name. We used this dataset as survival time data to reproduce tables 2-3 and figure 3: specifically for the analysis of clinical events and composite events.

hivanadat_new.dta contains variables such as the site ID, ID, the randomization arm (treatment or control), biological sex, CD4 absolute, etc. for 1775 HIV-1 uninfected participants. This dataset contains survival time data wherein the failure variables are those with "event" in the name, the duration variables are those with "dura" in the name, and the exit dates are those with "_dt" in the name. We also used this dataset as survival time data to reproduce tables 2-3 and figure 3 for the analysis of linked transmission and any transmission of HIV-1.

2.2 Statistical methods

We followed the statistical methods used in Cohen et al. (2011) to conduct the pure replication. Specifically, as in the original paper, in order to conduct the primary analysis consisting to determine the impact of early therapy on the primary prevention endpoint, as the original authors, we used the Kaplan-Meier method to calculate event-free probabilities and person-year analysis for incidence rate for a given year. We also used the Cox regression to estimate relative risks (expressed as hazard ratios and 95% confidence intervals) and adjustment for potential prognostic factors such as the infected

participant's baseline CD4 count, baseline plasma HIV-1 RNA concentration, and sex. The same Cox analyses were performed for outcomes of linked transmissions (genetically proven to have come from the partner), any transmissions (any new infection, from primary partner or other), clinical events, and composite monitoring events. The original authors used chi-square tests to compare the frequencies of adverse events. A p-value of less than 0.05 was considered statistically significant.

2.3 Pure replication results

2.3.1 Table 1: Baseline Characteristics of the Participants

We were able to replicate table 1 of the original paper presenting the baseline characteristic of the patients. Specifically, Table 1 shows that the replication results of demographic and clinical characteristics of patients are identical of those presented in the original with only one exception. In our pure replication, we found that the number of observations of participants with plasma 100,001-1 million copies/ml is 182 whereas this number is 186 in the original paper. Aside from this difference, our baseline results are identical to those presented in the original paper. In addition, the baseline characteristics of the patients are balanced between the two study arms, confirming the original results.

Table 1: Baseline Characteristics of the Participants

	HIV-1 --Infected Participants				HIV-1--Uninfected Participants			
	Original Early Therapy (N=886)	Replication Early Therapy (N=886)	Original Delayed Therapy (N=877)	Replication Delayed Therapy (N=877)	Original Early Therapy (N=893)	Replication Early Therapy (N=893)	Original Delayed Therapy (N=882)	Replication Delayed Therapy (N=882)
Demographic								
Female sex - no. (%)	432 (49)	432 (49)	441 (50)	441 (50)	441 (49)	441 (49)	418 (47)	418 (47)
Age group - no. (%)								
18-25 yr	145 (16)	145 (16)	161 (18)	161 (18)	154 (17)	154 (17)	174 (20)	174 (20)
26-40 yr	556 (63)	556 (63)	547 (62)	547 (62)	537 (60)	537 (60)	526 (60)	526 (60)
>40 yr	185 (21)	185 (21)	169 (19)	169 (19)	202 (23)	202 (23)	182 (21)	182 (21)
Education level - no. (%)								
No schooling	101 (11)	101 (11)	69 (8)	69 (8)	112 (13)	112 (13)	77 (9)	77 (9)
Primary schooling	360 (41)	360 (41)	347 (40)	347 (40)	317 (35)	317 (35)	344 (39)	344 (39)
Secondary schooling	346 (39)	346 (39)	388 (44)	388 (44)	373 (42)	373 (42)	367 (42)	367 (42)
Postsecondary schooling	79 (9)	79 (9)	72 (8)	72 (8)	91 (10)	91 (10)	93 (11)	93 (11)
Missing data	0	0	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Marital status - no. (%)								
Single	49 (6)	49 (6)	38 (4)	38 (4)	53 (6)	53 (6)	43 (5)	43 (5)
Married or living with partner	833 (94)	833 (94)	833 (95)	833 (95)	834 (93)	834 (93)	833 (94)	833 (94)
Widowed, separated, or divorced	4 (<1)	4 (<1)	6 (1)	6 (1)	6 (1)	6 (1)	6 (1)	6 (1)
Region - no. (%)								
North or South America	142 (16)	142 (16)	136 (16)	136 (16)	145 (16)	145 (16)	139 (16)	139 (16)
Asia	267 (30)	267 (30)	264 (30)	264 (30)	268 (30)	268 (30)	264 (30)	264 (30)
Africa	477 (54)	477 (54)	477 (54)	477 (54)	480 (54)	480 (54)	479 (54)	479 (54)
Sexual activity- no. (%)								
Any unprotected sex in past week	37 (4)	37 (4)	51 (6)	51 (6)	49 (5)	49 (5)	53 (6)	53 (6)
No. of sex partners in past 3 mo								
0-1	831 (94)	831 (94)	833 (95)	833 (95)	863 (97)	863 (97)	844 (96)	844 (96)
2 - 4	48 (5)	48 (5)	41 (5)	41 (5)	29 (3)	29 (3)	36 (4)	36 (4)

>4	7 (1)	7 (1)	2 (<1)	2 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Missing Data	0	0	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
No. of sexual encounters in past week								
0	246 (28)	246 (28)	225 (26)	225 (26)	253 (28)	253 (28)	240 (27)	240 (27)
1 - 2	430 (49)	430 (49)	438 (50)	438 (50)	410 (46)	410 (46)	433 (49)	433 (49)
3 - 4	156 (18)	156 (18)	158 (18)	158 (18)	180 (20)	180 (20)	151 (17)	151 (17)
>4	54 (6)	54 (6)	55 (6)	55 (6)	50 (6)	50 (6)	57 (6)	57 (6)
Missing Data	0	0	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Clinical								
CD4 count - no./mm^3								
Median	442	442	428	428				
Interquartile range	373-522	373-522	357-522	357-522	NA	NA	NA	NA
Plasma RNA viral load - no. (%)								
<400 copies/ml	54 (6)	54 (6)	43 (5)	43 (5)	NA	NA	NA	NA
400-1000 copies/ml	24 (3)	24 (3)	33 (4)	33 (4)	NA	NA	NA	NA
1001-10,000 copies/ml	212 (24)	212 (24)	183 (21)	183 (21)	NA	NA	NA	NA
10,001-100,000 copies/ml	407 (46)	407 (46)	432 (49)	432 (49)	NA	NA	NA	NA
100,001-1 million copies/ml	186 (21)	186 (21)	186 (21)	182 (21)	NA	NA	NA	NA
Missing Data	3 (<1)	3 (<1)	4 (<1)	4 (<1)	NA	NA	NA	NA
Women reporting previous antiretroviral therapy during pregnancy - no./total no(%)	115/432 (27)	115/432 (27)	119/441 (27)	119/441 (27)	NA	NA	NA	NA
Type of serodiscordancy - no. (%)								
HIV- positive man, HIV-negative woman	436 (49)	436 (49)	417 (48)	417 (48)	NA	NA	NA	NA
HIV- positive woman, HIV-negative man	431 (49)	431 (49)	441 (50)	441 (50)	NA	NA	NA	NA
HIV-positive man, HIV-negative man	18 (2)	18 (2)	19 (2)	19 (2)	NA	NA	NA	NA
HIV-positive woman, HIV-negative woman	1 (<1)	1 (<1)	0	0	NA	NA	NA	NA

Note: we shade results from the replication study to indicate discrepancies. we detected between the original results and results from the reanalysis.

2.3.2 Table 2: Incidence of Partner-Linked and Any HIV-1 Transmission and Clinical and Composite Events

Table 2 presents the incidence of Partner-Linked and Any HIV-1 Transmission and Clinical and Composite Events. As in the original results, in our replication we found that 28 transmissions were linked to the HIV-1–infected participant (incidence rate 0.9 per 100 person-years; 95% CI, 0.6 to 1.3), with 1 transmission in the early-therapy group (incidence rate, 0.1 per 100 person-years; 95% CI, 0.0 to 0.4) and 27 transmissions in the delayed-therapy group (incidence rate, 1.7 per100 person-years; % CI, 1.2 to 2.5), for a hazard ratio in the early-therapy group of 0.04 (95% CI, 0.01 to 0.27; P<0.001). Thus, this pure replication result is identical to the main finding of the original paper which found a relative reduction of 96% in the number of linked HIV-1 transmissions resulting from the early initiation of antiretroviral therapy, as compared with delayed therapy.

Moreover, as in the original paper, we analyse the impact of early therapy initiation by the duration of the follow up period. We found that on the 28 transmissions linked to the HIV-1 infected participant, in the early-therapy group 1 transmission (incidence rate, 0.1 per 100 person-years; 95% CI, 0.0 to 0.8) occurs among participants with a period of follow-up of 1 year, 0 transmission (incidence rate, 0.0 per 100 person-years; 95% CI, 0.0 to 0.0) occurs among participants with a period of follow-up between 2 and 3 years, and 0 transmission (incidence rate, 0.0 per 100 person-years; 95% CI, 0.0 to 0.0) occurs among participants with a period of follow up more than 3 years.

The number of transmissions by duration of the period of follow up we found is identical to the number of transmissions found in the original paper. However, although the rate of transmissions of events are identical to those found in the original paper, the confidence intervals are different for participants with a period of follow up between 2 and 3 years and participants with a period of follow up of more than 3 years as shown in Table 2. Stata is not able to calculate the confidence interval when the number of transmission event is equal to 0. In fact, the confidence intervals cannot be obtained from the formula of the confidence interval of the incidence rate when the number of transmission event.[1] Thus, it is not clear how the original authors obtained the confidence interval presented in the original paper.

Furthermore, in the delayed therapy, we found that the number of transmissions by the duration of period of follow-up is identical to the original results. However, although the rate of transmission events are also identical for different periods of duration of follow-up, our confidence intervals for participants with a period of follow of more than 3 years is different from the one found in the original study. This difference, which qualifies as a major difference, might be due to the way the confidence interval was calculated, as the original authors used SAS software. With the formula presented in the footnote 1, we obtained the replicated confidence interval obtained with Stata.[2] Finally, for the hazard ratio of follow-up more than 3 years, we find a major different between the original results and the results from the pure replication.

To conclude, for the pure replication of the 28 linked HIV-1 transmission, we were not able to replicate the confidence interval of the rate of transmissions of events for participants with a period of follow up more than 3 years, because Stata is not able to calculate the confidence interval when the transmission event is equal to 0. We find wider confidence intervals of the transmission rate and the hazard ratio for linked transmissions for participants with a period of follow up of more than 3 years than those found in the original paper results. However, these differences do not change one of the main results of the paper.

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[1] The 100(1-α) % confidence interval is of the incidence ratio is defined as:
$\left(e^{\ln r - z_{1-\frac{\alpha}{2}} SE}, e^{\ln r + z_{1-\frac{\alpha}{2}} SE}\right)$ Where: **1-α**: the two-sided confidence level; **a**: the number of clinical even; **N**: the person-time at risk; r: Incidence rate; SE the standard error

[2] To the best of my knowledge, there is a no standard definition of or rule of thumb for what major or minor difference means in replication. In this study, I classify a difference as major when the significance level of a coefficient changes or when the difference in effect size between the original results and the replication results is greater than 10 percent.

In our pure replication, we found that the hazard ratio in the early-therapy group of 0.04. As is the original paper, we found a relative reduction of 96% in the number of linked HIV-1 transmissions resulting from the early initiation of antiretroviral therapy, as compared with delayed therapy. Therefore, he wider confidence interval we found for the hazard ratio of participants with a follow-up of more than 3 years do not change the significance of the original paper result. As in the original paper, we found that the early-therapy has no impact on the linked HIV-1 transmissions for participants with a period of follow up of more than 3 years.

The results from the pure replication of the any transmissions mirror those found for the linked HIV-1 transmissions. Specifically, for the early therapy group, as the number of transmission event is equal to 0 for participants with a period of follow up of more than 3 years, Stata was not able to calculate the corresponding confidence interval. For the delayed therapy group, we found a wider interval confidence for participants with a period of follow up of more than 3 years. As result, we also found a wider confidence interval for participants with a period of follow up of more than 3 years. These differences do not change the results found in the original paper. As in the original paper, we found that for any HIV-1 transmissions, the hazard ratio in the early-therapy group of 0.11. This represents a relative reduction of 89% in the number of any HIV-1 transmissions resulting from the early initiation of antiretroviral therapy, as compared with delayed therapy.

In table 2, we also presented the results of the pure replication of the effect of the early therapy on clinical events.[3] For the early therapy group, we find a few differences. First, the number of clinical events for participants with a period of follow up between 2 and 3 years and participants with a period of follow up of more than 3 obtained in our pure replication is slightly different to those presented in the original paper results. We found 28 events after 1 year and 10 events after 2-3 years, whereas the original authors found 29 and 9, respectively. This might be due to a difference in the classification of one participant. Consequently, the total number of person-years for participants with a period of follow up between 2 and 3 years is different from what was found by the original authors. As the result of this difference, the point estimate and the confidence interval of the hazard ratio in the early-therapy group are larger for participants with a period of follow up between 2 and 3 years and participants with a period of follow up of more than 3 compared than those found in the original paper.

For clinical events, we found that the hazard ratio in the early-therapy group of 0.60 (95% CI, 0.41 to 0.90; P=0.01). This represents a relative reduction of 41% in the number of clinical events resulting from the early initiation of antiretroviral therapy, as compared with delayed therapy. This is very similar to the value found by the original authors. They found the hazard ratio in the early-therapy group of 0.59 (95% CI, 0.40 to 0.88; P = 0.01). We found a difference of 0.5 percentage points in the hazard ratio for the early-therapy for participants with a period of follow up between 2 to 3 years. The corresponding confidence interval of this hazard ratio is wider in comparison to the one found by the original authors. This led to a lack of statistical significance of the early-therapy among participants with a period of follow up between 2 and 3 years, whereas it was statistically significant in the original paper. However, this finding was just barely significant, as the upper end of the confidence interval was close to 1.

Finally, in Table 2, we present the pure replication results of the impact of the early-therapy on the composite events.[4] For the early therapy group, we found the same number of composite events as in the original paper. However, the total number of person-years for different groups from our pure replication is different from the numbers presented in the original paper, especially for the groups of the total participant and the participants with a period of follow up between 2 and 3 years. As the result, we found minor differences between the incidence rates from our pure replication and the original paper results. For the delayed therapy group, although the number of composite events we found is identical to the original findings, the total number of person-years is different in our

[3]Clinical events include death, World Health Organization stage 4 events, severe bacterial infections, and pulmonary tuberculosis for index partners.
[4] Composite events include death or World Health Organization stage 4 events (excluding esophageal candidiasis) for the index partner or HIV transmission to the uninfected partner, whichever occurred earlier.

replication from the original paper. This difference can be considered as a major difference for two groups: the total participants and for participants with a period of follow up between 2 and 3 years. This leads to a minor difference on the hazard ratio between our pure replication and the original paper results for this time interval, although the significance remains unchanged. As in the original study we found an identical hazard ratio in the early-therapy group of 0.28 (95% CI, 0.18 to 0.45; P<0.001). Furthermore, we find very similar ratios for participants with different periods of follow up.

Through our replication of Figure 1, we discovered that 57 HIV-1-uninfected participants and 9 HIV-1-infected participants were missing values for the duration, thus forcing Stata to drop the variables from the survival time analysis. This is explained in more detail below, however its important to note that this could be the cause of some discrepancies between the original results and the replication in Table 2.**Table 2: Incidence of Partner-Linked and Any HIV-1 Transmission and Clinical and Composite Events.**

	Early Therapy						Delayed Therapy							
	Original Events	Rep Events	Original Person-yr	Rep Person-yr	Original Rate (95% CI)	Rep Rate (95% CI)	Orignal Events	Rep Events	Orignal Person-yr	Rep Person-yr	Orignal Rate (95% CI)	Rep Rate (95% CI)	Orignal Hazard or Rate Ratio (95% CI)	Rep Hazard or Rate Ratio (95% CI)
Linked Transmission														
Total	1	1	1585.3	1585.3	0.1 (0.0-0.4)	0.1 (0.0-0.4)	27	27	1567.3	1567.3	1.7 (1.1-2.5)	1.7 (1.2-2.5)	0.04 (0.01-0.27)	0.04 (0.01-0.27)
1 yr	1	1	819	819	0.1 (0.0-0.7)	0.1 (0.0-0.8)	16	16	813.3	813.3	2.0 (1.1-3.2)	2.0 (1.2-3.2)	0.06 (0.00-0.40)	0.06 (0.00-0.40)
2-3 yr	0	0	686.5	686.5	0.0 (0.0-0.5)	0.0 .	9	9	682.8	682.8	1.3 (0.6-2.5)	1.3 (0.7-2.5)	0.00 (0.00-0.50)	0.00 (0.00-0.50)
>3 yr	0	0	79.9	79.9	0.0 (0.0-4.6)	0.0 .	2	2	71.2	71.2	2.8 (0.3-10.1)	2.8 (0.7-11.2)	0.00 (0.00-4.75)	0.00 (0.00-5.18)
Any transmission														
Total	4	4	1585.3	1585.3	0.3 (0.1-0.6)	0.3 (0.1-0.7)	35	35	1567.3	1567.3	2.2 (1.6-3.1)	2.2 (1.6-3.1)	0.11 (0.04-0.32)	0.11 (0.04-0.32)
1 yr	2	2	819	819	0.2 (0.0-0.9)	0.2 (0.1-1.0)	18	18	813.3	813.3	2.2 (1.3-3.5)	2.2 (1.4-3.5)	0.11 (0.01-0.46)	0.11 (0.01-0.46)
2-3 yr	2	2	686.5	686.5	0.3 (0.0-1.1)	0.3 (0.1-1.2)	14	14	682.8	682.8	2.1 (1.1-3.4)	2.1 (1.1-3.5)	0.14 (0.02-0.62)	0.14 (0.02-0.62)
>3 yr	0	0	79.9	79.9	0.0 (0.0-4.6)	0.0 .	3	3	71.2	71.2	4.2 (0.9-12.3)	4.2 (1.4-13.1)	0.00 (0.00-2.16)	0.00 (0.00-2.35)
Clinical events														
Total	40	40	1661.9	1661.9	2.4 (1.7-3.3)	2.4 (1.8-3.3)	65	65	1641.8	1641.8	4.0 (3.1-5.0)	4.0 (3.1-5.0)	0.59 (0.40-0.88)	0.61 (0.41-0.90)
1 yr	29	28	831	831.9	3.5 (2.3-5.0)	3.4 (2.3-4.9)	39	39	832.6	832.6	4.7 (3.3-6.4)	4.7 (3.4-6.4)	0.75 (0.44-1.24)	0.73 (0.43-1.22)
2-3 yr	9	10	739.8	739.8	1.2 (0.6-2.3)	1.2 (0.6-2.3)	21	21	725.7	725.7	2.9 (1.8-4.4)	2.9 (1.9-4.4)	0.42 (0.17-0.96)	0.47 (0.20-1.04)
>3 yr	2	2	91.1	91.1	2.2 (0.3-7.9)	2.2 (0.3-7.9)	5	5	83.6	83.6	6.0 (1.9-14.0)	6.0 (2.5-14.4)	0.37 (0.04-2.24)	0.39 (0.04-2.41)
Composite events														
Total	23	23	1700.1	1692.5	1.4 (0.9-2.0)	1.4 (0.9-2.0)	79	79	1642	1632.5	4.8 (3.8-6.0)	4.8 (3.8-6.0)	0.28 (0.18-0.45)	0.28 (0.18-0.45)

1 yr	13	13	843.7	841.5	1.5 (0.8-2.6)	1.5 (0.9-2.7)	47	47	833.9	832	5.6 (4.1-7.5)	5.6 (4.2-7.5)	0.27 (0.14-0.51)	0.30 (0.15-0.56)
2-3 yr	8	8	763.8	758.6	1.0 (0.5-2.1)	1.1 (0.5-2.1)	26	26	732.5	725.5	3.5 (2.3-5.2)	3.6 (2.4-5.3)	0.30 (0.12-0.67)	0.30 (0.12-0.68)
>3 yr	2	2	92.6	92.4	2.2 (0.3-7.8)	2.2 (0.5-8.7)	6	6	75.5	75	7.9 (2.9-17.3)	8.0 (3.6-17.8)	027 (0.03-1.52)	0.30 (0.03-1.68)

Note: we shade results from the replication study to indicate discrepancies we detected between the original results and results from the reanalysis. NA denotes not applicable.

2.3.3 Figure 1: Kaplan–Meier Estimates for Partner-Linked and Any HIV-1 Transmission and for Clinical and Composite Monitoring Events

We used the Kaplan–Meier method to replicate Figure 1, using the same methods as the original study to produce unadjusted survival curves between the two study arms (Figure 1)[5]. This is a nonparametric method to calculate the cumulative survival over time, considering differing risk sets at each time point with individuals lost to follow-up, still at risk, or having already experienced the outcome (Kaplan and Meier 1958).

Figures A and B, which are the Kaplan-Meier estimates for HIV-1 uninfected participants, in panel 1 (original results) are in general similar in shape to figures in panel 2 (replication results). However, there is a major difference in the number of observations between the two sets of results. Figure A of the panel 1 shows that the total number of participants at risk at year 0 since randomization is 1775, however our replication shows 1718 observations at risk at year 0 (a difference of 57 observations). We conducted an investigation into the causes of this discrepancy, which showed that 57 observations in the data set provided by the original authors have missing data on the duration of the follow up period (survival time).

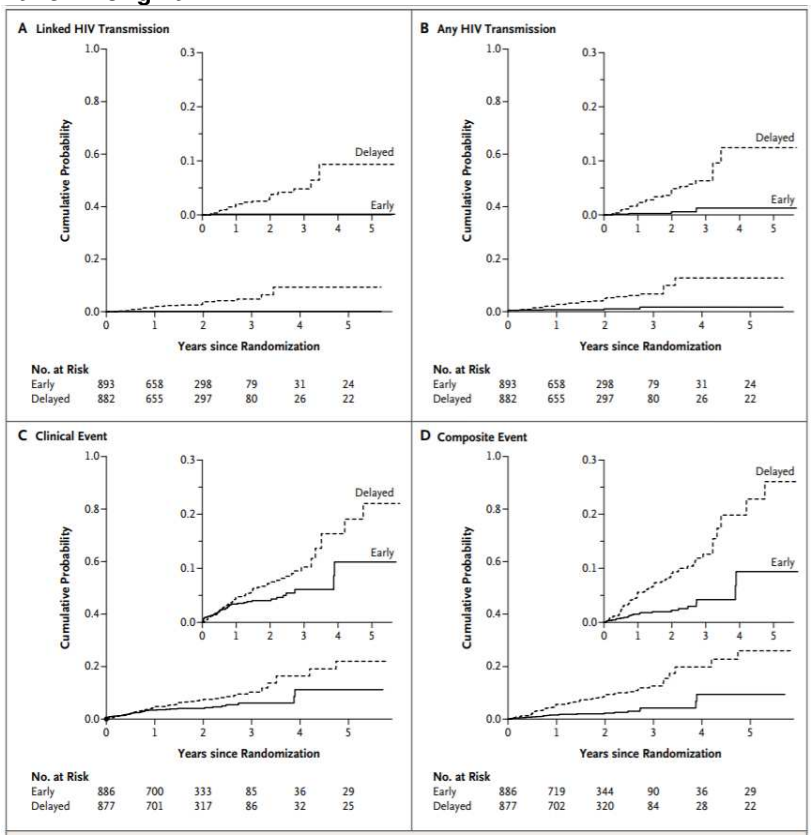
Similarly, figures C and D, which are the Kaplan-Meier estimates for HIV-1 infected participants, appear to have similar graphs between the original results (panel 1) and the replicated results (panel 2), however the numbers also differ due to a similar reason as above. The original paper starts with 1,763 observations at year 0 while the results from our replication start with 1,754 observations at year 0. This is a difference of 9 observations. We conducted a similar investigation as before and found that the duration data is missing for these 9 observations.

Thus, it is unclear how the original authors were able to obtain the original results of the panel 1 with missing duration values for 57 HIV-1 uninfected participants and 9 HIV-1 infected participants. Without the duration values for these observations, Stata do not include the observations in the survival time analysis to calculate the Kaplan–Meier estimates used for the graphical representation. This accounts for the differences in values of the risk tables associated with each graph. As stated above, this is the likely cause of the discrepancies in Table 2, as well.

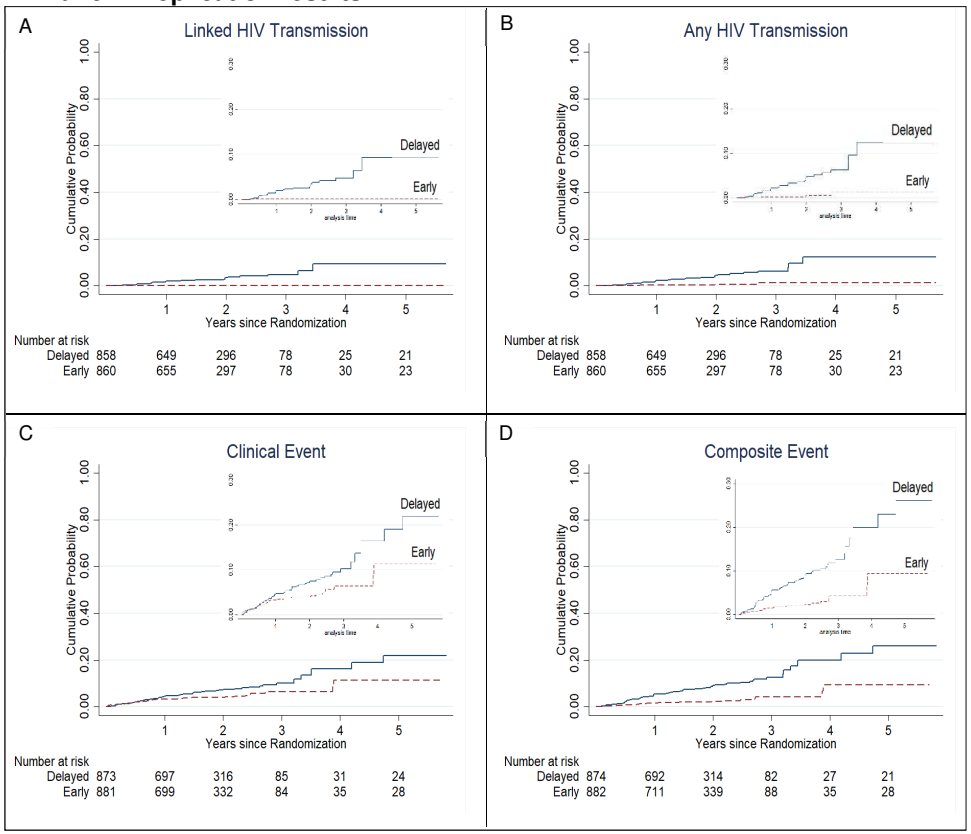
[5] The original paper has two figures; however, we are unable to replicate the first figure, representing the trial profile, because we lack information recruitment of couples from the general population, randomization, HIV-1–uninfected partner's enrolment, seroconversion at baseline, retention, and loss-to-follow-up for assessment of the primary end point of linked HIV-1 transmission.

Figure 1: Kaplan–Meier Estimates for Partner-Linked and Any HIV-1 Transmission and for Clinical and Composite Monitoring Events

Panel 1: original



Panel 2: replication results



Note: Author's construction using the data from the original authors. Panel A original from [Figure 2. Kaplan–Meier Estimates for Partner-Linked and Any HIV-1 Transmission and for Clinical and Composite Monitoring Event] in Cohen and colleagues (2011).

2.3.4 Table 3: Hazard Ratios for prognostic factors for partner-linked and any HIV-1 transmission and for clinical and composite events

Table 3 presents the pure replication results of hazard ratios for prognostic factors for partner-linked and any hiv-1 transmission and for clinical and composite events. As in the original paper, we used univariate and multivariate Cox regression analyses, stratified according to study site to estimate relative risks expressed as hazard ratios and 95% confidence intervals. This assessed the difference in the infected participant's baseline CD4 count, baseline plasma HIV- 1 RNA concentration, sex, and the baseline condom use on four events: linked transmissions, any transmissions, clinical events, and composite monitoring events. This analysis adjusts for potential prognostic factors including the infected participant's baseline CD4 count, baseline plasma HIV- 1 RNA concentration, sex, and the baseline condom use.

Results of the univariate analysis from our pure replication are identical to the original paper results. For example, one of the results show the baseline CD4 count is higher for the infected participant of the linked HIV-1 transmission participants. Another result is that the probability of using the condom at the baseline is significant lower the linked HIV-1 transmission participants. Regarding the impact of the early therapy on linked transmissions, any transmissions, clinical events, and composite monitoring events adjusting for potential prognostic factors, the results of our pure replication are identical from the original paper results except in two cases were the differences are very minor.

In fact, these results show that the main results of the paper do not change even when adjusting for potential prognostic factors. As in the univariate analysis, we found the hazard ratios in early-therapy group of 0.04, 0.11, 0,59, and 0.28 for linked HIV-1 transmissions, any HIV-1 transmissions, the clinic events, and the composite events (respectively). This represents a relative reduction of 96%, 89%, 41%, and 72% in the number of linked HIV-1 transmissions, any HIV-1 transmissions, clinic events, and the composite events (respectively), resulting from the early initiation of antiretroviral therapy, as compared with delayed therapy.

Table 3: Hazard Ratios for prognostic factors for partner-linked and any HIV-1 transmission and for clinical and composite events

Univariate analysis	Original Linked transmission	Replication Linked transmission	Original Any transmission	Replication Any transmission	Original Clinical events	Replication Clinical events	Original Composite events	Replication Composite events
Early therapy vs. delayed therapy	0.04 (0.01-0.26)	0.04 (0.01-0.26)	0.11 (0.04-0.32)	0.11 (0.04-0.32)	0.60 (0.41-0.90)	0.60 (0.41-0.90)	0.28 (0.18-0.45)	0.28 (0.18-0.45)
Baseline CD4 count (per 100 CD4 increment)	1.27 (1.02-1.59)	1.27 (1.02-1.59)	1.25 (1.02-1.52)	1.25 (1.02-1.52)	0.84 (0.70-1.00)	0.84 (0.70-1.00)	1.06 (0.91-1.24)	1.06 (0.91-1.24)
Baseline viral load (per unit log10 increment)	1.96 (1.17-3.27)	1.96 (1.17-3.27)	1.66 (1.08-2.55)	1.66 (1.08-2.55)	1.74 (1.32-2.30)	1.74 (1.32-2.30)	1.51 (1.15-1.97)	1.51 (1.15-1.97)
Male sex vs. female sex	0.69 (0.31-1.52)	0.69 (0.31-1.52)	0.88 (0.45-1.71)	0.88 (0.45-1.71)	1.61 (1.05-2.48)	1.61 (1.05-2.48)	1.18 (0.78-1.78)	1.18 (0.78-1.78)
Baseline condom use (100% vs. <100%)	0.35 (0.14-0.88)	0.35 (0.14-0.88)	0.47 (0.19-1.14)	0.47 (0.19-1.14)	NA	NA	0.68 (0.29-1.60)	0.68 (0.29-1.60)
Multivariate analysis								
Early therapy vs. delayed therapy	0.04 (0.01-0.28)	0.04 (0.01-0.28)	0.11 (0.04-0.33)	0.11 (0.04-0.33)	0.59 (0.40-0.89)	0.59 (0.40-0.89)	0.28 (0.18-0.45)	0.28 (0.18-0.45)
Baseline CD4 count (per 100 CD4 increment)	1.24 (1.00-1.54)	1.24 (1.00-1.54)	1.22 (1.02-1.47)	1.22 (1.02-1.47)	0.90 (0.75-1.08)	0.90 (0.75-1.08)	1.11 (0.96-1.28)	1.11 (0.96-1.28)
Baseline viral load (per unit log10 increment)	2.85 (1.51-5.41)	2.85 (1.51-5.40)	2.13 (1.30-3.50)	2.13 (1.30-3.50)	1.65 (1.24-2.20)	1.65 (1.24-2.19)	1.60 (1.21-2.11)	1.60 (1.21-2.11)
Male sex vs. female sex	0.73 (0.33-1.65)	0.73 (0.32-1.65)	1.00 (0.51-1.97)	1.00 (0.51-1.97)	1.46 (0.95-2.26)	1.46 (0.95-2.26)	1.18 (0.78-1.80)	1.18 (0.78-1.80)
Baseline condom use (100% vs. <100%)	0.33 (0.12-0.91)	0.33 (0.12-0.91)	0.41 (0.16-1.08)	0.41 (0.16-1.08)	NA	NA	0.64 (0.27-1.52)	0.64 (0.27-1.52)

Note: we shade results from the replication study to indicate discrepancies we detected between the original results and results from the reanalysis. NA denotes not applicable.
Source: Authors' Construction using the data from the original authors.

2.4 Pure replication conclusions

In this pure replication of Cohen and colleagues' study (2011), we used data shared by the original authors to apply the same methods as the original paper. We were able to replicate most of the tables and the overall trajectory of the figure included in the original paper. We found minor differences mostly from table 2 presenting the main results of the original paper and a major difference in the number of participants used for creating the figures that displays the main results of the paper. Specifically, the differences found are related to the fact that the pure replication results show different hazard ratio and associated confidence interval for primary prevention outcome, primary treatment outcome and composite monitoring events for participants with a period of follow up between 2 and 3 years and participants with a period of follow up of more than 3 years. It is difficult to explain why we found these minor differences, they might be due to the missing data on survival time on some observations, and some of them might also be due to the utilization of different software to produce findings presented in the original paper and findings presented in our pure replication. However, we think that the utilisation of different software should have a minimal effect on the results.

We note that these minor differences between our pure replication and the original paper results did not change the statistical significance of these findings, which were not statistically significant in the original paper in most cases. The major difference found in our pure replication was number of participants at risk at 0 year since randomization. In our pure replication, in the figure displaying the main results, we find that there are missing duration values for 57 HIV-1 uninfected participants and 9 HIV-1 infected participants from the dataset shared with us by the original authors. Although this difference did not fundamentally change the nature of the Kaplan-Meier graphs, the associated risk tables contain major differences.

In this pure replication, we were able to reproduce the main results of the original paper. As in the original paper, our replication shows a relative reduction of 96% in the number of linked HIV-1 transmissions resulting from the early initiation of antiretroviral therapy, as compared with delayed therapy.

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