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Treatment as prevention

A replication study on early antiretroviral therapy initiation and HIV-1 transmission

June 2020

Replication Paper 24

Health

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Treatment as prevention: a replication study on early antiretroviral therapy initiation and HIV-1 transmission

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Summary

Early antiretroviral therapy (ART) of an HIV-1-infected individual has been shown to lower the risk of transmitting HIV to his or her uninfected partner, as first shown in the study known as HPTN052 published by Cohen and colleagues (2011). It had been common practice to delay ART until an individual's CD4 count fell below a specific level; however, based on the HPTN052 study and other studies, the World Health Organization recommended that anyone infected with HIV-1 should begin ART as soon after diagnosis as possible.

This paper presents a replication study of the HPTN052 study by Cohen and colleagues using the data shared by the original authors. First, applying the methods described in the original paper, we conducted a pure replication. We were able to replicate most of the tables and the shape of the figures included in the original paper. However, we found a major difference in the number of observations (i.e. participants) used to create the figures that display the main results of the paper (Figures 2A–2D in the original paper).

However, this major difference does not change the conclusions of the original paper. We also found minor differences elsewhere, mostly in Table 2 of the original paper. The discrepancies found between the replication and the original study 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 of participants between year intervals differs.

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 for the most part were not statistically significant in the original paper. As in the original paper, our replication shows a relative reduction of 96 per cent in the number of linked HIV-1 transmissions resulting from early initiation of ART, as compared with delayed therapy.

In the subsequent measurement and estimation analyses, we divided the total number of participants into two subgroups: participants from African nations only and participants from non-African nations only. We found that early initiation of ART still reduced rates of sexual transmission of HIV-1 and clinical events when considering the participants from the African nations only. However, due to the lack of statistical power given the reduced sample size, there are no conclusive results for the subgroup of participants from non-African nations only.

When clustering the standard errors by site, we find the same effect size for hazard ratios for multiple outcomes. However, the confidence intervals are narrower, showing that the statistical significance of the estimates is improved. We were not able to control for male circumcision because the original authors declined to share the data of male circumcision with us.

Similarly, we were unable to study the relationship between ART adherence and the impact of early initiation of ART, given that the original authors also declined to share the relevant data. Finally, we assess the Cox proportional hazards assumption in two ways: examining time-dependent covariates and using Schoenfeld residuals. We found that the Cox proportional hazards assumption is met for all outcomes and the covariates used in the analyses.

This study and recent studies rigorously test the impact of early initiation of ART, showing it to be effective in reducing HIV-1 transmission in trial studies. Other recent studies show the limited effectiveness of universal testing and treatment due to poor linkage to care. Therefore, we suggest that future research on early initiation of ART should test how to improve the linkage to care for HIV-1-infected patients.

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Abbreviations and acronyms

ART	Antiretroviral therapy
MEA	Measurement and estimation analysis
PMTCT	Prevention of mother-to-child transmission
WHO	World Health Organization

1. Introduction

Since September 2015, the 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, such that all populations and age groups are now eligible for immediate treatment.

Previously, the WHO recommendation was to initiate ART once an individual's CD4 cell count dropped below a certain level. A person's CD4 cell count corresponds to a number of cells per cubic millimetre, with sicker individuals having lower counts. The WHO-specified threshold CD4 cell 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 randomised controlled trials that showed improved health 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 and colleagues (2011) which aimed to assess whether, in addition to benefiting the patient, early initiation of ART could lower the risk of an HIV-1-infected individual transmitting HIV-1 to his or her uninfected partner. Cohen and colleagues (2011) enrolled 1,763 HIV-1 serodiscordant (one partner is HIV-1-infected and the other is HIV-1-uninfected) 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).

Enrolment took place from June 2007 to 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 ART, except for short-term prevention of mother-to-child transmission of HIV-1.

After enrolment, HIV-1 serodiscordant couples were randomly assigned, in a 1:1 ratio, to receive ART immediately (early therapy group, n = 886), or to receive it after a decline in CD4 count (two consecutive measurements of 250 or less) or the development of an illness related to AIDS (delayed therapy group, n = 877). The primary prevention endpoint was genetically linked HIV-1 transmission in HIV-1-uninfected partners. The primary clinical endpoint was the earliest occurrence of pulmonary tuberculosis, severe bacterial infection, a WHO stage 4 event, or death. Cohen and colleagues (2011), through an individual randomisation trial, determined 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-uninfected partners. Specifically, the authors find that 39 HIV-1 transmissions occurred since enrolment. Of these, 28 transmissions were biologically linked to the HIV-infected partners. Of the 28 linked transmissions, only one occurred in the early therapy group. This difference represents a relative reduction of 96 per cent due to early initiation of ART ($p < 0.001$).

Furthermore, the authors find that for the serious HIV-1-related clinical events (i.e. a WHO stage 4 event, severe bacterial infection or pulmonary tuberculosis, or death)

observed in the HIV-1-infected partners, 40 were in the early therapy group and 65 in the delayed therapy group (hazard ratio 0.59; 95% confidence interval [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 per cent in the early therapy group and 14 per cent 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 indicating that early ART was associated with a 96 per cent lower risk to linked HIV-1 transmissions. 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 a prevention approach at the population level (Hayes et al. 2017; Iwuji et al. 2018; Amanyire et al. 2016). As such, HPTN052 was a seminal study in suggesting that 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 underscore 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 the methods used and to produce the results presented in the original paper. We present the pure replication as the first part of the replication of the study of Cohen and colleagues (2011). Specifically, we present the data used, the methods used by the original authors as well as 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 were provided by Cohen and colleagues (2011) at 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® version 15.1, which we used to conduct the pure replication.

The dataset *index.dta* contains the data used for analysis of baseline characteristics of HIV-1-infected participants. It contains information about 1,763 individuals including demographic (age, sex, sexual activity and region) and clinical data (plasma RNA viral load and type of serodiscordancy). 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 the original Table 1 (our Table 2).

The dataset *partner.dta* contains similar baseline demographic data as *index.dta*, but for 1,775 HIV-1-uninfected participants. The dataset *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-1-uninfected participants.

It is unclear in the materials provided by Cohen and colleagues what the difference is between PMDsex and IDMsex. We used this dataset for the reproduction of the findings for HIV-1-uninfected participants in the original Table 1 (our Table 2).

The dataset *othanadat_new.dta* contains other information for the 1,763 HIV-1-infected individuals, including variables such as the site ID, ID, the randomisation arm (treatment or control), biological sex and CD4 absolute count. 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 and 3 and Figure 2 from the original paper (our Tables 3 and 4 and Figure 1), specifically for the analysis of clinical events and composite events.

HIVanadat_new.dta contains other information for the 1,775 HIV-1-uninfected participants, including variables such as the site ID, ID, the randomisation arm (treatment or control), biological sex and CD4 absolute count. 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 and 3 and Figure 2 from the original paper (our Tables 3 and 4 and Figure 1), specifically for the analysis of linked transmission and any transmission of HIV-1. Our Table 1 presents the full details of the variables used in this paper.

Table 1: Detailed presentation of different variables used for the pure replication

Dataset	Variable name	Description	N	Dataset	Variable name	Description	N
index.dta: HIV-1-infected participants Used for the original Table 1 (our Table 2)				*partner.dta: HIV-1-uninfected participants Used for the original Table 1 (our Table 2)*			
	iid	ID number	1,763		iid	ID number	1,775
	site	Site ID	1,763		site	Site ID	1,775
	sitename	Site name	1,763		sitename	Site name	1,775
	randarm	Randomisation arm	1,763		IDMsex	Biological sex	1,775
	IDMsex	Biological sex	1,763		age	Age at enrolment	1,775
	age	Age at enrolment	1,763		randarm	Randomisation arm	1,775
	edstat	Education level	1,762		edstat	Education level	1,774
	marstat	Marital status	1,763		marstat	Marital status	1,775
	region	Region	1,763		region	Region	1,775
	cduse	Condom use in the past week	1,762		cduse	Condom use in the past week	1,774
	npcat	No. of sexual partners in the past 3 months	1,762		npcat	No. of sexual partners in the past 3 months	1,774
	nsacat	No. of sexual encounters in past week	1,762		nsacat	No. of sexual encounters in past week	1,774
	IEVcd4cl	CD4 absolute count	1,752				
	rnacatt	Plasma RNA viral load	1,756				
	IENartpt	Previous ART use during pregnancy	810				
	part_type	Type of serodiscordancy	1,763				
othanadat_new.dta: HIV-1-infected participants Used for the original Tables 2 and 3 and Figure 2 (our Tables 3 and 4 and Figure 1)				*HIVanadat_new.dta: HIV-1-uninfected participants Used for the original Tables 2 and 3 and Figure 2 (our Tables 3 and 4 and Figure 1)*			
	iid	ID number	1,763		iid	ID number	1,775
	site	Site ID	1,763		site	Site ID	1,775
	randarm	Randomisation in envelope	1,763		randarm	Randomisation in envelope	1,775
	comp_dt	Date of composite event	1,756		hivstat	HIV transmission	1,722
	compevent	Composite event	1,763		hiv_dt	Date of HIV transmission	1,722
	rx_dt	Date of clinical event	1,754		dura_hiv	Duration to HIV transmission	1,718
	rxevent	Clinical event	1,763		linkhiv	Linked HIV transmission	1,722
	death_dt	Date of death	1,754		ifvcd4cl	CD4 absolute count	1,764
	death	Death event	1,763		ifvicdt	Initial collection date	1,774
	dura_rx	Duration to clinical event	1,753		ifvrna	Copies RNA PCR/plasma	1,768
	dura_comp	Duration to composite event	1,756		part_type	Type of serodiscordancy	1,775
	dura_death	Duration to death	1,754		log10rna	Baseline viral load	1,768
	linkcomp	Linked HIV transmission	1,763		cduse	Baseline condom use	1,774
	log10rna	Baseline viral load	1,756		PDMsex	Biological sex, for original Table 1 (our Table 2)	1,775
	cduse	Baseline condom use	1,762		IDMsex	Biological sex, for original Tables 2 and 3 (our Tables 3 and 4)	1,775
	IDMsex	Biological sex	1,763		cd4	Baseline CD4 count	1,764
	cd4	Baseline CD4 count	1,752				

Source: Authors' construction using the data from the original authors.

2.2 Statistical methods

We followed the statistical methods used in Cohen and colleagues (2011) to conduct the pure replication. Specifically, in order to conduct the primary analysis to determine the impact of early therapy on the primary prevention endpoint (as in the original study), 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 HIV-1-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 (HIV transmissions that were genetically proven to have come from the partner), any transmissions (any new HIV-1 infection, from primary partner or other), clinical events and composite 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 Original Table 1: Baseline characteristics of the participants

We were able to replicate Table 1 of the original paper presenting the baseline characteristics of the patients. Specifically, our Table 2 shows that the replication results for the demographic and clinical characteristics of patients are identical to 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 to 1 million copies per millilitre is 182, whereas this number was 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 (the early therapy group and the delayed therapy group), confirming the original results.[1]

[1] Although balance tests were not presented in the original paper, we conducted balance tests for all baseline characteristics presented in our Table 2. We used a t-test for continuous variables and the Pearson chi-square test for categorical variables. All the baseline characteristics are perfectly balanced, except for education ($p = 0.04$ for HIV-1-infected participants and $p = 0.07$ for HIV-1-uninfected participants).

Table 2: 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 years	145 (16)	145 (16)	161 (18)	161 (18)	154 (17)	154 (17)	174 (20)	174 (20)
26–40 years	556 (63)	556 (63)	547 (62)	547 (62)	537 (60)	537 (60)	526 (60)	526 (60)
> 40 years	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)
Post-secondary 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 months								
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)

	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)
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
400–1,000 copies/ml	24 (3)	24 (3)	33 (4)	33 (4)	NA	NA	NA	NA
1,001–10,000 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 re-analysis.
Source: Authors' construction using the data from the original authors.

2.3.2 Original Table 2: Incidence of partner-linked HIV-1 transmission, any HIV-1 transmission, clinical events and composite events

Our Table 3 presents the incidence of partner-linked HIV-1 transmission, any HIV-1 transmission, clinical events and composite events. As in the original results, our replication found that 28 transmissions were linked to the HIV-1-infected partner, 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 per 100 person-years; 95% CI, 1.2 to 2.5), with a hazard ratio 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 per cent in the number of linked HIV-1 transmissions resulting from early initiation of ART as compared with delayed therapy.

Moreover, as in the original paper, we analyse the impact of early ART initiation by the duration of the follow-up period. We found that for 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) occurred among participants with a period of follow-up of 1 year; 0 transmissions (incidence rate, 0.0 per 100 person-years; 95% CI, 0.0 to 0.0) occurred among participants with a period of follow-up of between 2 and 3 years; and 0 transmissions (incidence rate, 0.0 per 100 person-years; 95% CI, 0.0 to 0.0) occurred among participants with a period of follow-up of 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 rates of transmission events are identical to those found in the original paper, the confidence intervals are different for participants with a period of follow-up of between 2 and 3 years, and participants with a period of follow-up of more than 3 years, as shown in our Table 3.

Stata® is not able to calculate the confidence interval when the number of transmission events is equal to zero. In fact, the confidence intervals cannot be obtained from the formula of the confidence interval of the incidence rate when the number of transmission events is equal to zero.[2] Thus, it is not clear how the original authors obtained the confidence interval presented in the original paper.

Furthermore, in the delayed therapy group, we found that the number of transmissions by the duration of period of follow-up is identical to the original results. However, although the rates of transmission events are also identical for different periods of duration of follow-up, our confidence intervals for participants with a period of follow-up of more than three years is different from the one found in the original study.

This difference, which qualifies as a major difference,[3] might be due to the way in which the confidence interval was calculated, as the original authors used SAS® software. With the

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[2] The 100(1-α)% confidence interval 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** is the two-sided confidence level; **a** is the number of clinical events; **N** is the person-time at risk; r is the incidence rate; and SE is the standard error.

[3] To the best of our knowledge, there is no standard definition for what constitutes a major or minor difference in replication. In this study, we 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 per cent.

formula presented in footnote 2, we obtained the replicated confidence interval obtained with Stata®. Finally, for the hazard ratio of follow-up of more than three years, we find a major difference between the original results and the results from the pure replication.

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

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

The results from the pure replication of the outcome of any transmissions of HIV-1 mirror those found for the linked transmissions. Specifically, for the early therapy group, as the number of transmission events is equal to zero for participants with a period of follow-up of more than three years, Stata® is 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 three 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 was 0.11. This represents a relative reduction of 89 per cent in the number of any HIV-1 transmissions resulting from early initiation of ART, as compared with delayed therapy.

In our Table 3, we also present the results of the pure replication for the effect of early therapy on clinical events.[4] For the early therapy group, we found a few differences. First, the number of clinical events for participants with a period of follow-up of between 2 and 3 years, and participants with a period of follow-up of more than 3 years, obtained in our pure replication is slightly different to those presented in the original paper results.

We found 28 clinical events after 1 year and 10 clinical 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 of between 2 and 3 years is different from what was found by the original authors.

[4] Clinical events include death, WHO stage 4 events, severe bacterial infections and pulmonary tuberculosis for the HIV-1-infected partner.

As a result of this difference, the point estimate and the confidence interval of the hazard ratio in the early therapy group are larger than those found in the original paper for participants with a period of follow-up of between 2 and 3 years and participants with a period of follow-up of more than 3 years.

For clinical events, we found that the hazard ratio was 0.61 (95% CI, 0.41 to 0.90; p = 0.01). This represents a relative reduction of 41 per cent in the number of clinical events resulting from the early initiation of ART, as compared with delayed therapy. This is very similar to the value found by the original authors. They found that the hazard ratio in the early therapy group was 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 of between 2 and 3 years.

The corresponding confidence interval of this hazard ratio is wider in comparison with the one found by the original authors. This led to a lack of statistical significance for early therapy among participants with a period of follow-up of between two and three 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 one.

Finally, in our Table 3, we present the pure replication results for the impact of the early therapy on the composite events.[5] For the early therapy group, we found the same number of composite events as the original paper. However, the total number of person-years for different groups in our pure replication is different from the numbers presented in the original paper, especially for the groups of total participants and participants with a period of follow-up of between two and three years. As a result, we found minor differences between the incidence rates in the results of our pure replication and the original paper.

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 replication than the original paper. This difference can be considered a major difference for two groups: total participants and participants with a period of follow-up of between two and three years.

This leads to a minor difference in 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 2 in the original paper, 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, it is important to note that this could be the cause of some discrepancies between the original results in Table 2 and the replication in our Table 3.

[5] Composite events include death or WHO stage 4 events (excluding oesophageal candidiasis) for the HIV-1 infected partner or HIV transmission to the uninfected partner, whichever occurred earlier.

Table 3: Incidence of partner-linked and any HIV-1 transmission and clinical and composite events

	Early therapy						Delayed therapy							
	Original Events	Rep Events	Original Person-year	Rep Person-year	Original Rate (95% CI)	Rep Rate (95% CI)	Original Events	Rep Events	Original Person-year	Rep Person-year	Original Rate (95% CI)	Rep Rate (95% CI)	Original Hazard or rate ratio (95% CI)	Rep Hazard or rate ratio (95% CI)
Linked transmission														
Total	1	1	1,585.3	1,585.3	0.1 (0.0–0.4)	0.1 (0.0–0.4)	27	27	1,567.3	1,567.3	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 year	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 years	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 years	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	1,585.3	1,585.3	0.3 (0.1–0.6)	0.3 (0.1–0.7)	35	35	1,567.3	1,567.3	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 year	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 years	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 (1.2–3.5)	0.14 (0.02–0.62)	0.14 (0.02–0.62)
> 3 years	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	1,661.9	1,664.3	2.4 (1.8–3.3)	2.4 (1.8–3.3)	65	65	1,641.8	1,641.8	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 year	29	28	831	832.0	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 years	9	10	739.8	741.3	1.3 (0.7–2.5)	1.3 (0.7–2.5)	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 years	2	2	91.1	91.1	2.2 (0.5–8.7)	2.2 (0.5–8.8)	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	1,700.1	1,692.5	1.4 (0.9–2.0)	1.4 (0.9–2.0)	79	79	1,642	1,632.5	4.8 (3.8–6.0)	4.8 (3.9–6.0)	0.28 (0.18–0.45)	0.28 (0.18–0.45)
1 year	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 years	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 years	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: Rep = replication study. We shade results from the replication study to indicate discrepancies we detected between the original results and results from the re-analysis.

Source: Authors' construction using the data from the original authors.

2.3.3 Original Figure 2: Kaplan–Meier estimates for partner-linked and any HIV-1 transmission and for clinical and composite events

We used the Kaplan–Meier method to replicate Figure 2 of the original paper (our Figure 1), using the same methods as the original study to produce unadjusted survival curves for the two study arms.[6] This is a nonparametric method to calculate the cumulative survival over time, considering different risk sets at each time point of individuals being lost to follow-up, still at risk or having already experienced the outcome (Kaplan and Meier 1958).

Figures 1A and 1B below are the Kaplan–Meier estimates for HIV-1-uninfected participants. The figures in panel 1 (original results) are generally similar in shape to those in panel 2 (replication results); however, there is a major difference in the number of observations between the two sets of results. Figure 1A in panel 1 shows that the total number of participants at risk at year 0 since randomisation is 1,775, yet our replication in panel 2 shows 1,718 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 dataset provided by the original authors have missing data on the duration of the follow-up period (survival time).

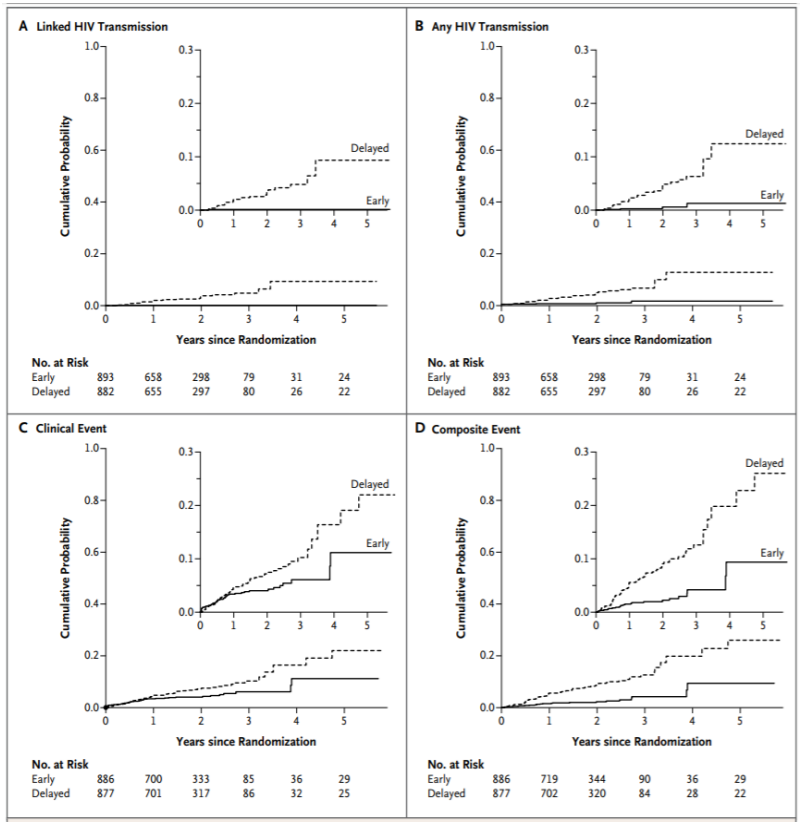
Similarly, Figures 1C and 1D below – which are the Kaplan–Meier estimates for HIV-1-infected participants – appear to have similar graphs in the original results (panel 1) and the replicated results (panel 2); however, the numbers also differ, for a similar reason to above. The original paper starts 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 to that for uninfected participants 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 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® does 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 the original Table 2 (our Table 3) as well.

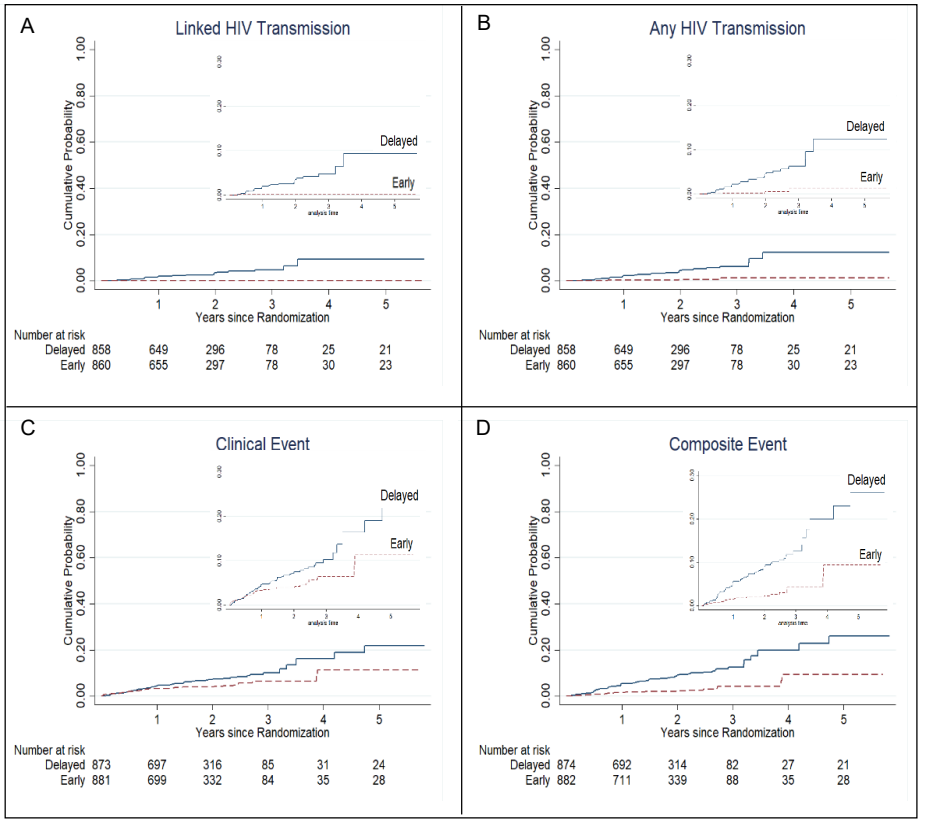
[6] The original paper has two figures; however, we are unable to replicate the original Figure 1 on enrolment and outcomes because we lack information on: recruitment of couples from the general population; randomisation; HIV-1-uninfected partner's enrolment; seroconversion at baseline; retention; and loss-to-follow-up for assessment of the primary endpoint of linked HIV-1 transmission.

Figure 1: Kaplan–Meier estimates for partner-linked and any HIV-1 transmission and for clinical and composite events

Panel 1: Original results



Panel 2: Replication results



Source: Panel 1 (original results) from Cohen and colleagues (2011). Panel 2 (replication results) construction using the data from the original authors.

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

Our Table 4 presents the pure replication results for hazard ratios of 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 per cent 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 events. This analysis adjusts for potential prognostic factors, including the infected participant's baseline CD4 count, baseline plasma HIV-1 RNA concentration, sex and baseline condom use.

The results of the univariate analysis from our pure replication are identical to the original paper results. For example, one of the results shows that the baseline CD4 count is higher for the original HIV-1-infected partner in the instances of linked HIV-1-transmission. Another result is that the probability of using condoms at baseline is significantly lower for the linked HIV-1 transmission participants.

Regarding the impact of early therapy on linked HIV-1 transmissions, any transmissions, clinical events and composite events (adjusting for potential prognostic factors), the results from our pure replication are identical to the original paper results, except in two cases where the differences are very minor.

In fact, these findings 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 hazard ratios due to early therapy initiation of 0.04, 0.11, 0.59, and 0.28 for linked HIV-1 transmissions, any HIV-1 transmissions, clinical events and 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, clinical events and composite events, respectively, resulting from early initiation of ART, as compared with delayed therapy.

Table 4: Hazard ratios of 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)	0.03 (0.00–0.26)	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)	2.86 (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: NA = not applicable. We shaded results from the replication study to indicate discrepancies we detected between the original results and results from the re-analysis. 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 figures included in the original paper. We found minor differences, mostly in the original Table 2 presenting the main results of the original paper, and a major difference in the number of participants used to create the figures that display the main results of the paper (Figures 2A–2D in the original paper).

Specifically, the differences found are related to the fact that the pure replication results show a different hazard ratio and associated confidence interval for primary prevention outcome, primary treatment outcome and composite events for participants with a period of follow-up of 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 for some observations, and some might also be due to the utilisation of different software to produce the findings presented in the original paper and those 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 the number of participants at risk at year zero since randomisation.

In our pure replication of the original Figure 2 (displaying the main results), we find (see our Figure 1) 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 per cent in the number of linked HIV-1 transmissions resulting from early initiation of ART, as compared with delayed therapy.

3. Measurement and estimation analysis

Although Cohen and colleagues (2011) conducted a thorough analysis, we conducted additional robustness checks to test the strength of their conclusions. In this section, we present the results of the measurement and estimation analysis (MEA). First, we conducted a subgroup analysis by region (African or non-African) to determine whether the impact of early therapy on sexual transmission of HIV-1 among HIV-1-uninfected partners is different by region.

Second, we conducted robustness checks to examine if patients from the same site[7] might lack independence (Kloek 1981; Moulton 1986). Although the authors stratified by site in the multivariate Cox regression, we clustered the standard errors by site to account for potential intra-site correlation. Next, we tested the Cox proportional hazards assumption using two methods: examining time-dependent covariates and using Schoenfeld residuals (Schoenfeld 1982). All analysis in the MEA, as in the pure replication, was done using Stata® version 15.1.

Two of our planned analyses in the MEA were not possible, given that the original authors declined to provide the relevant data. First, as male circumcision has been found to reduce HIV transmission by about 60 per cent (Auvert et al. 2005; Bailey et al. 2007; Gray et al. 2007), we planned to control for the male circumcision status that might significantly affect the hazard ratio for the effect of early ART on HIV-1 transmission to uninfected men. Finally, in order to better understand how early initiation of ART affects sexual transmission of HIV-1, we planned to assess whether the effect of early initiation of ART on rates of sexual transmission of HIV-1 varies by the level of adherence to ART.

3.1 Differences by region (African or non-African)

3.1.1 African nations only

A study by Abu-Raddad and colleagues (2013) reported higher viral loads in patients with HIV-1 infection in Sub-Saharan Africa compared with infected patients in other regions of the world. The HPTN052 study found that a high viral load at baseline is associated with an increased risk of HIV-1 transmission, and that 82 per cent of the new HIV-1 transmissions occurred in Africa even though only 54 per cent of all study participants were enrolled from this region.

This suggests that there may have been different baseline viral loads by region within the HPTN052 study. It is possible that the protective effect of treatment could differ by region and by average baseline viral load. In order to test this hypothesis, we conducted two separate subgroup analyses. First, we separated the total group of participants into two subgroups: participants from African countries and participants from non-African countries. Then we replicated Table 2 and Figure 2 of the original paper for these two subgroups, using the analytic approaches (the Kaplan–Meier method and the Cox regression) used in the original paper.

Our Table 5 presents the incidence of partner-linked HIV-1 transmission, any HIV-1 transmission, clinical events and composite events only for the subgroup of participants from Africa. We found that 23 transmissions were linked to the HIV-1-infected participants, with 1 transmission in the early therapy group (incidence rate 0.1 per 100 person-years; 95% CI, 0.0 to 1.0) and 22 transmissions in the delayed therapy group (incidence rate 3.19 per 100 person-years; 95% CI, 2.1 to 4.8), for a hazard ratio in the early therapy group of 0.04 (95% CI, 0.005 to 0.31; $p < 0.01$).

Thus, when we restrict the participants to the subgroup from Africa only, the result is identical to the main findings of the original paper, which found a relative reduction of 96 per cent in the number of linked HIV-1 transmissions resulting from early initiation of

[7] The study was conducted in 9 countries at 13 sites.

ART, as compared with delayed therapy. In fact, this result shows that the higher viral load in patients infected with HIV-1 in Sub-Saharan Africa has no impact on the effect of early ART initiation on HIV-1 transmission.

Moreover, as in the original paper, we analysed the impact of early therapy initiation by the duration of the follow-up period only on the subgroup of participants from Africa. We found that for the 23 transmissions linked to HIV-1-infected participants in the early therapy group, 1 transmission (incidence rate 0.23 per 100 person-years; 95% CI, 0.03 to 1.64) occurs among participants with a period of follow-up of 1 year; 0 transmissions (incidence rate 0.0 per 100 person-years; 95% CI, 0.0 to 0.0) occur among participants with a period of follow-up of between 2 and 3 years; and 0 transmissions (incidence rate 0.0 per 100 person-years; 95% CI, 0.0 to 0.0) occur among participants with a period of follow-up of more than 3 years.

This is similar to the results for the total group, as is the relative risk reduction. The relative risk reduction due to the early therapy is 93 per cent among participants with a period of follow-up of one year in the subgroup of participants from Africa, whereas it is 94 per cent for participants from all regions.

This subgroup analysis by region on any transmission of HIV-1 mirrors that found for linked HIV-1 transmission. Specifically, we found 3 transmissions in the early therapy group (incidence rate 0.4 per 100 person-years; 95% CI, 0.1 to 1.3) and 29 transmissions in the delayed therapy group (incidence rate 4.2 per 100 person-years; 95% CI, 2.9 to 6.0), for a hazard ratio of 0.10 (95% CI, 0.03 to 0.32; $p < 0.01$).

Thus, we find a relative reduction of 90 per cent in the number of any HIV-1 transmissions for participants who received early initiation of ART, compared with delayed therapy. This is very similar to what we found when considering participants from all regions.

Next, we present the results of this subgroup analysis on clinical events and composite events (our Table 5). The proportion of participants from Africa with clinical events (45%) is lower than the proportion of participants from Africa in the total group of all regions (54%). However, the proportion of participants from Africa with composite events (57%) is similar to the proportion of participants from Africa in the total group (54%).

Despite the minor difference in the proportion of participants for clinical events in the early therapy group, the incidence rate of clinical events (2.5 per 100 person-years; 95% CI, 1.57 to 3.86) is similar to the rate found in the original paper when considering the total group of all regions (2.4 per 100 person-years; 95% CI, 1.70 to 3.35). This is also the case when considering the delayed therapy group.

Furthermore, we find a hazard ratio in the early therapy group of 0.66 (95% CI, 0.37 to 1.19) for the subgroup from Africa, while the hazard ratio in the early therapy group for the participants from all regions is 0.59 (95% CI, 0.40 to 0.88). Given the broader confidence intervals, we cannot conclude if early therapy has a protective effect against clinical events for African participants, while we could conclude this for participants from all regions.

For composite events, the incidence rate (1.40 per 100 person-years; 95% CI, 0.80 to 2.5) for participants from Africa in the early therapy group is similar to the incidence rate found in the original paper when considering all regions (1.40 per 100 person-years; 95% CI, 0.90 to 2.00). The same is true when we consider delayed therapy. The hazard ratio in the early therapy group for composite events for the subgroup from Africa only is 0.22 (95% CI, 0.11 to 0.42), which is relatively close to the hazard ratio for the early therapy group from all regions (0.28; 95% CI, 0.18 to 0.45).

Furthering this subgroup analysis by region, we used the Kaplan–Meier method on just the participants from Africa to produce our Figure 2, using the same methods as the original study to produce unadjusted survival curves for the two study arms. Figures 2A and 2B are the Kaplan–Meier estimates for the cumulative probabilities in the early and delayed therapy groups of linked HIV-1 transmission between partners, and any HIV transmission, respectively.

The figures in panel 1 (original results) are generally close in shape to panel 2 (African nations only). Similarly, Figures 2C and 2D show the Kaplan–Meier estimates for the cumulative probabilities of clinical events and composite events. The figures in panel 1 (original results) are also close in shape to panel 2 (African nations only).

To conclude, we find that early therapy is still effective in reducing HIV transmission when restricting the group of participants to those from Africa. The HPTN052 study found that a high viral load at baseline is associated with an increased risk of HIV transmission, and that 82 per cent of the new HIV-1 transmissions occurred in participants from Africa, who represented only 54 per cent of all participants enrolled in this study.

Importantly, the relative risk reduction when restricting the participants to the subgroup from Africa is similar to what is found in the original paper with participants from all regions. Thus, we can conclude that despite the high viral load of HIV patients in Africa, early therapy is associated with a 94 per cent lower risk of linked HIV-1 transmission.

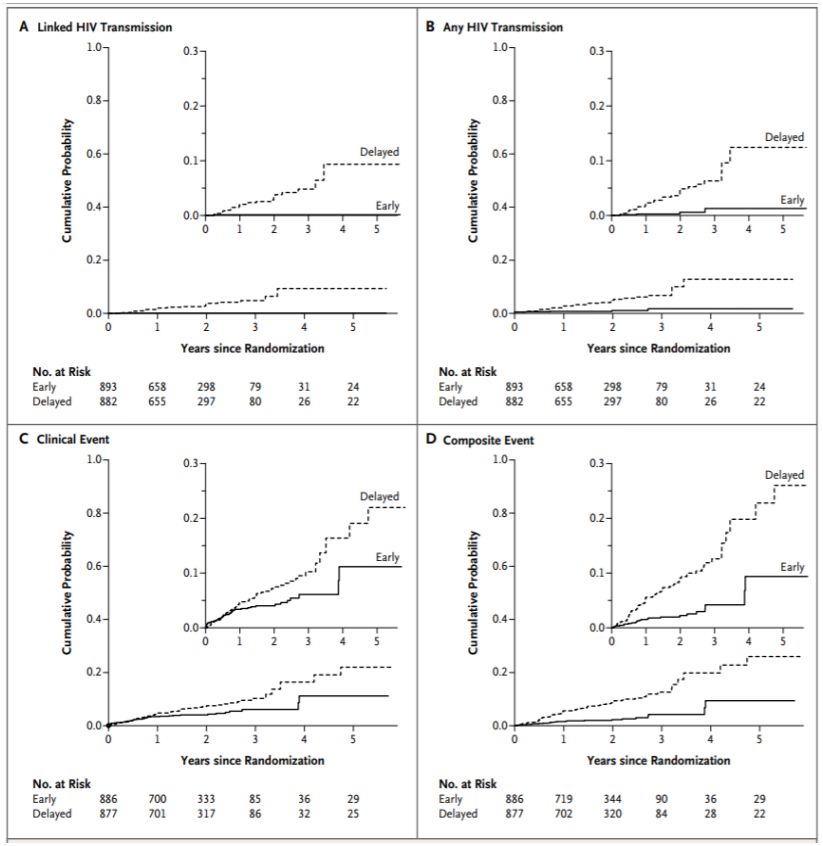
Table 5: Incidence of partner-linked and any HIV-1 transmission and clinical and composite events (African nations only)

	Early therapy			Delayed therapy			
	Events	Person-year	Rate (95% CI)	Events	Person-year	Rate (95% CI)	Hazard or rate ratio (95% CI)
Linked transmission							
Total	1	718	0.1 (0.0–1.0)	22	690.7	3.19 (2.1–4.8)	0.04 (0.01–0.31)
1 year	1	431.9	0.2 (0.0–1.6)	15	428.8	3.5 (2.1–5.8)	0.07 (0.00–0.48)
2–3 years	0	261.9	0.0	5	250.3	2.0 (0.8–4.8)	0.00 (0.00–1.1)
> 3 years	0	24.3	0.0	2	11.6	17.2 (4.3–68.9)	0.00 (0.00–3.3)
Any transmission							
Total	3	718	0.4 (0.1–1.3)	29	690.7	4.2 (2.9–6.0)	0.10 (0.03–0.32)
1 year	2	431.9	0.4 (0.1–1.9)	16	428.8	3.7 (2.3–6.1)	0.14 (0.02–0.60)
2–3 years	1	261.9	0.4 (0.1–2.7)	10	250.3	4.0 (2.1–7.4)	0.10 (0.00–0.69)
> 3 years	0	24.3	0.0	3	11.6	25.8 (8.3–80.1)	0.00 (0.00–1.49)
Clinical events							
Total	19	770.5	2.5 (1.6–3.9)	28	752.8	3.7 (2.6–5.4)	0.66 (0.37–1.19)
1 year	16	444.5	3.6 (2.2–5.9)	22	445.8	4.9 (3.2–7.5)	0.87 (0.43–1.74)
2–3 years	2	297.9	0.7 (0.2–2.7)	3	283.7	1.1 (0.3–3.3)	0.64 (0.05–5.5)
> 3 years	1	28.1	3.6 (0.5–25.2)	3	23.2	12.9 (4.2–39.9)	0.30 (0.01–3.76)
Composite events							
Total	11	782.1	1.4 (0.8–2.5)	47	737.3	6.4 (4.8–8.5)	0.22 (0.11–0.42)
1 year	6	450.1	1.3 (0.6–3.0)	32	444.1	7.2 (5.1–10.2)	0.24 (0.08–0.58)
2–3 years	4	303.7	1.3 (0.5–3.5)	11	276.7	4.0 (2.2–7.2)	0.34 (0.08–1.1)
> 3 years	1	28.3	3.5 (0.5–25.1)	4	16.5	24.3 (9.1–64.8)	0.17 (0.00–1.73)

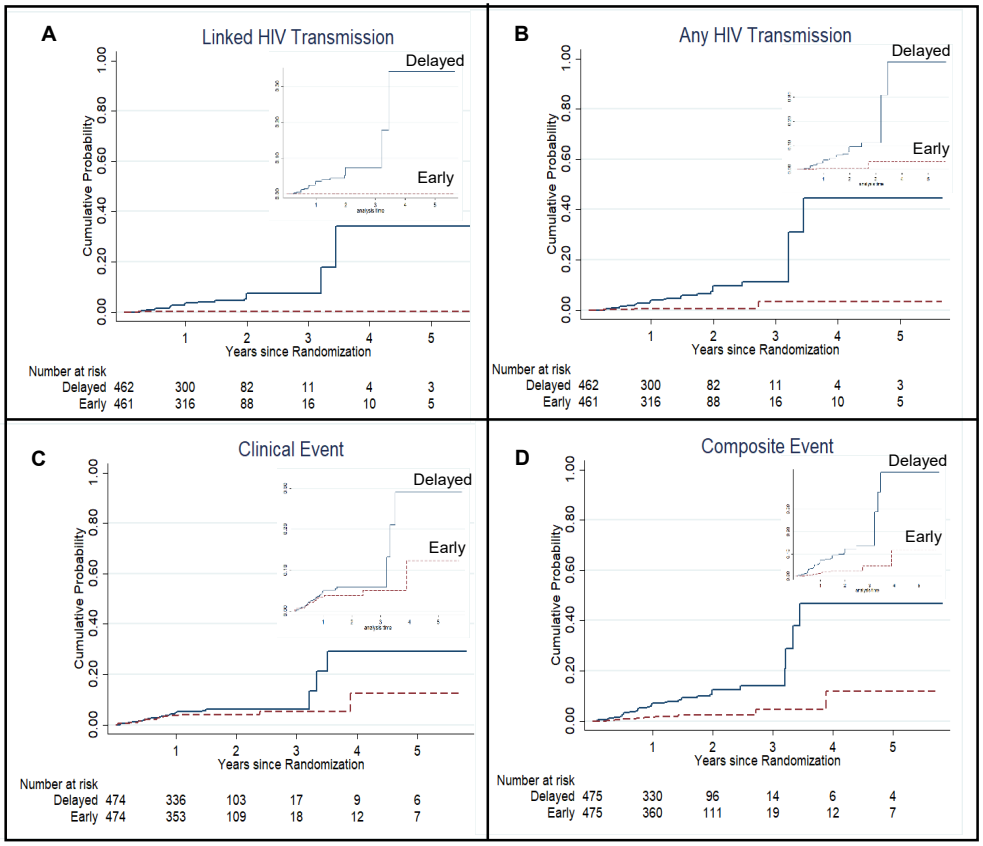
Source: Authors' construction using the data from the original authors.
Blank cells denote a result of '.' from Stata®

Figure 2: Kaplan–Meier estimates for partner-linked and any HIV-1 transmission and for clinical and composite events (African nations only)

Panel 1: Original results



Panel 2: Replication results



Source: Panel 1 (original results) from Cohen and colleagues (2011). Panel 2 (replication results) authors' construction using the data from the original authors.

3.1.2 Non-African nations

Our Table 6 presents the incidence of partner-linked HIV-1 transmission, any HIV-1 transmission, clinical events and composite events for a subgroup of participants from non-African nations. We found that 5 transmissions were linked to HIV-1-infected participants (incidence rate 0.28 per 100 person-years; 95% CI, 0.12 to 0.70), with 0 transmissions in the early therapy group (incidence rate 0 per 100 person-years; 95% CI, 0 to 0) and 5 transmissions in the delayed therapy group (incidence rate 0.57 per 100 person-years; 95% CI, 0.24 to 1.37), for a hazard ratio of 1.91e-16 (95% CI, 0 to ; $p < 0.01$).[8]

Thus, when we restrict the participants to the subgroup from non-African nations only, the result is very different from the main finding presented in the original paper. In fact, we find a non-significant relative reduction of 100 per cent in the number of linked HIV-1 transmissions resulting from early initiation of ART, as compared with delayed therapy. These results, if significant, would imply that in a context of lower viral loads in patients with HIV-1 infection in non-African nations, the early ART initiation on HIV-1 transmission might not be effective.

The results from the replication of the 'any transmissions' outcome on non-African participants show that early ART initiation is not effective in reducing HIV-1 transmission. Specifically, we found 1 transmission in the early therapy group (incidence rate 0.11 per 100 person-years; 95% CI, 0.02 to 0.82) and 6 transmissions in the delayed therapy group (incidence rate 0.69 per 100 person-years; 95% CI, 0.31 to 1.52), for a hazard ratio of 0.17 (95% CI, 0.02 to 1.4; $p < 0.1$).

In short, we find that early initiation of ART has no impact on any HIV-1 transmissions. This finding indicates that, in a context of lower viral loads in patients, the total number of HIV-1 transmissions resulting from early initiation of ART (regardless of viral linkage with the infected partner) is not impacted.

Table 6 shows that the proportion of participants from non-African nations with clinical events (55%) is higher than the proportion of participants from non-African nations in the total group of all regions (46%). However, the proportion of participants from non-African nations with composite events (43%) is similar to the proportion of participants from non-African nations in the total group (46%).

Despite this minor difference in the proportion of participants with clinical events, in the early therapy group the incidence rate of clinical events for non-African participants (2.35 per 100 person-years; 95% CI, 1.53 to 3.60) is similar to the rate for the total group (2.4 per 100 person-years; 95% CI, 1.70 to 3.35). This is also the case when considering the delayed therapy group.

Furthermore, the hazard ratio for clinical events of participants from non-African nations is 0.56 (95% CI, 0.33 to 0.96), while the hazard ratio for the total group of participants from all regions is 0.59 (95% CI, 0.40 to 0.88). This finding suggests that early therapy has a protective effect against clinical events on participants from non-African nations.

[8] The analysis produced a CI of 0 to ., denoted above by blank from Stata®.

Additionally, the incidence rate (1.31 per 100 person-years; 95% CI, 0.74 to 2.32) of composite events of non-African participants in the early therapy group is similar to what we found (1.40 per 100 person-years; 95% CI, 0.90 to 2.00) in the early therapy group for the total group from all regions. The same is true when we consider the delayed therapy. Finally, the hazard ratio for the composite events for non-African participants is 0.37 (95% CI, 0.19 to 0.71), which is higher than the relative risk reduction (0.28; 95% CI, 0.18 to 0.45) found for the total group.

We used the Kaplan–Meier method on just the participants from non-African nations to produce our Figure 3, using the same methods as the original study to produce unadjusted survival curves for the two study arms. Figures 3A and 3B are the Kaplan–Meier estimates for the cumulative probabilities of linked HIV-1 transmission between partners and any transmission in the early therapy and delayed therapy groups, respectively.

The shape of the figures in panel 2 (non-African nations) is very different from the shape of the figures in panel 1 (African nations only) for linked HIV transmission and any HIV transmission. This is an illustration of the lack of impact of early initiation therapy on HIV-1 transmission outside Africa. Moreover, Figures 3C and 3D (which are the Kaplan–Meier estimates for the cumulative probabilities of clinical events and composite events among participants in the early therapy and delayed therapy groups) show that when restricting the group of participants to those from non-African nations (panel 2), the results are also close in shape to the original results (panel 1). In short, the Kaplan–Meier estimates show a lack of statistically significant impacts of early ART initiation on HIV-1 transmission.

To conclude, we did not find statistically significant results indicating whether early ART initiation is effective in reducing HIV-1 transmission when restricting the analysis to participants from non-African nations. Importantly, while the relative risk reduction when restricting the participants to the subgroup from non-African nations is higher than for the total group, it is not statistically significant for linked HIV-1 transmission or any transmission of HIV-1. We want to stress that this lack of impact is likely to be due to a low statistical power when restricting the participants to those from non-African countries.

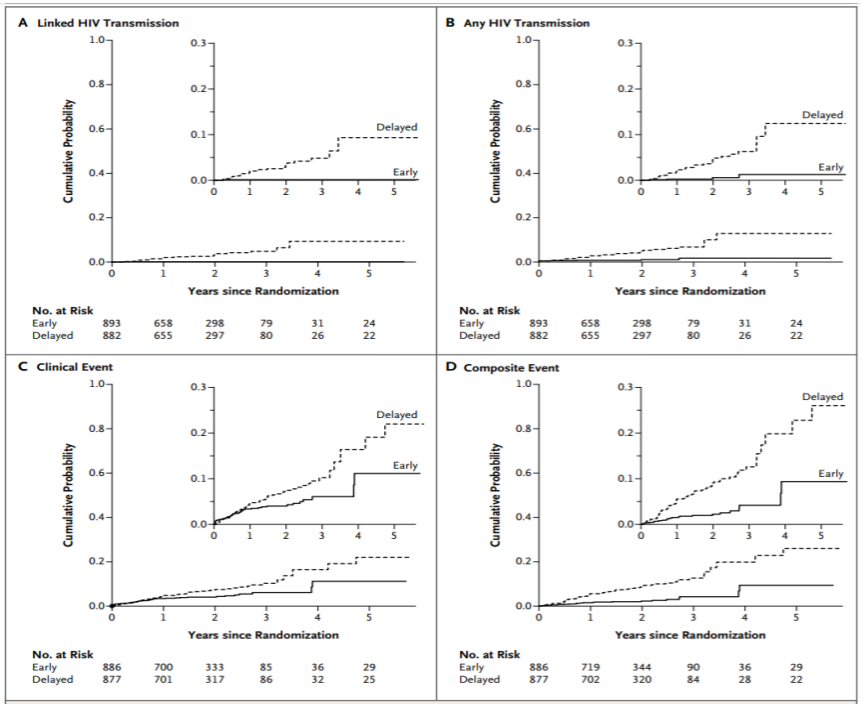
Table 6: Incidence of partner-linked and any HIV-1 transmission and clinical and composite events (non-African nations only)

	Early therapy			Delayed therapy			
	Events	Person-year	Rate (95% CI)	Events	Person-year	Rate (95% CI)	Hazard or rate ratio (95% CI)
Linked transmission							
Total	0	867.3	0.0	5	876.6	0.6 (0.2–1.4)	1.91 e-16 (0.00–)
1 year	0	387.1	0.0	1	384.4	0.3 (0.0–1.8)	0.00 (0.00–28.75)
2–3 years	0	424.6	0.0	4	432.5	0.9 (0.3–2.5)	0.00 (0.00–1.52)
> 3 years	0	55.6	0.0	0	59.6	0.0	
Any transmission							
Total	1	867.3	0.1 (0.0–0.8)	6	876.6	0.7 (0.3–1.5)	0.17 (0.02–1.40)
1 year	0	819	0.0 (0.0–0.0)	2	384.4	0.5 (0.1–2.1)	0.00 (0.00–3.92)
2–3 years	1	686.5	0.2 (0.0–2.5)	4	432.5	0.9 (0.3–2.5)	0.25 (0.01–2.54)
> 3 years	0	79.9	0.0 (0.0–0.0)	0	59.6	0.0	
Clinical events							
Total	21	893.8	2.3 (1.5–3.6)	37	889.0	4.2 (3.0–5.7)	0.56 (0.33–0.96)
1 year	12	387.5	3.1 (1.8–5.5)	17	386.8	4.4 (2.7–7.1)	0.44 (0.19–0.97)
2–3 years	8	443.3	1.8 (0.9–3.6)	18	442.0	4.1 (2.6–6.5)	0.45 (0.17–1.09)
> 3 years	1	63.0	1.6 (0.2–11.3)	2	60.3	3.3 (0.8–13.3)	0.51 (0.01–9.7)
Composite events							
Total	12	910.4	1.3 (0.7–2.3)	32	895.2	3.6 (2.5–5.1)	0.37 (0.19–0.71)
1 year	7	391.5	1.8 (0.9–3.8)	15	387.9	3.9 (2.3–6.4)	0.30 (0.10–0.78)
2–3 years	4	454.9	0.9 (0.3–2.3)	15	448.7	3.3 (2.0–5.5)	0.27 (0.7–0.85)
> 3 years	1	64.1	1.6 (0.2–11.1)	2	58.6	3.4 (0.9–13.7)	0.48 (0.01–9.31)

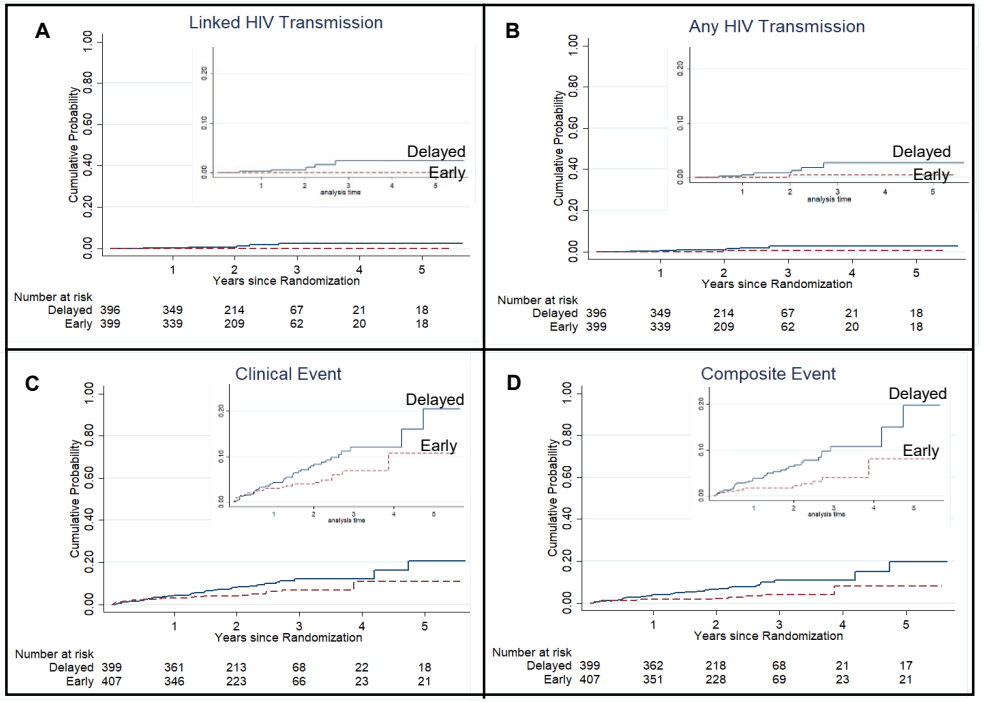
Source: Authors' construction using the data from the original authors. Blank cells denote a result of '.' from Stata®.

Figure 3: Kaplan–Meier estimates for partner-linked and any HIV-1 transmission and for clinical and composite events (non-African nations only)

Panel 1: Original results



Panel 2: Replication results



Source: Authors' construction using the data from the original authors.

3.2 Clustering

We conduct additional robustness checks to examine if patients from the same site might lack independence (Kloek 1981; Moulton 1986). Although the authors stratified by site in the multivariate Cox regression in the HPTN052 study, this does not correct for intra-site correlation. To account for this, we cluster the standard errors by site, as there were 13 sites in 9 countries. To check the robustness of the main results, we replicate the main results (our Table 3), clustering the standard errors by site ID using the command 'cluster' in Stata®.

As expected, we find the same effect size of hazard ratios for prognostic factors for partner-linked and any HIV-1 transmission and clinical and composite events (our Table 7). However, the standard errors have narrower confidence intervals, indicating a possible intra-site correlation. In addition to an increased significance level, clustering rendered baseline condom use (100% versus < 100%) from insignificant (95% CI, 0.19 to 1.14) to significant (0.31 to 0.71).

Table 7: Hazard ratios for prognostic factors for partner-linked transmission, any HIV-1 transmission, clinical events and composite events (clustering)

	Original	Adjusted for clustering	Original	Adjusted for clustering	Original	Adjusted for clustering	Original	Adjusted for clustering
	Linked transmission	Linked transmission	Any transmission	Any transmission	Clinical events	Clinical events	Composite events	Composite events
Univariate analysis								
Early therapy vs. delayed therapy	0.04 (0.01–0.26)	0.03 (0.01–0.19)	0.11 (0.04–0.32)	0.11 (0.06–0.22)	0.60 (0.41–0.90)	0.60 (0.42–0.86)	0.28 (0.18–0.45)	0.28 (0.20–0.41)
Baseline CD4 count (per 100 CD4 increment)	1.27 (1.02–1.59)	1.27 (1.16–1.40)	1.25 (1.02–1.52)	1.25 (1.14–1.37)	0.84 (0.70–1.00)	0.84 (0.63–1.10)	1.06 (0.91–1.24)	1.06 (0.92–1.22)
Baseline viral load (per unit log10 increment)	1.96 (1.17–3.27)	1.96 (1.52–2.51)	1.66 (1.08–2.55)	1.66 (1.25–2.21)	1.74 (1.32–2.30)	1.74 (1.37–2.23)	1.51 (1.15–1.97)	1.51 (1.15–1.98)
Male sex vs. female sex	0.69 (0.31–1.52)	0.69 (0.40–1.17)	0.88 (0.45–1.71)	0.88 (0.53–1.46)	1.61 (1.05–2.48)	1.61 (1.20–2.17)	1.18 (0.78–1.78)	1.18 (0.78–1.79)
Baseline condom use (100% vs. < 100%)	0.35 (0.14–0.88)	0.35 (0.25–0.47)	0.47 (0.19–1.14)	0.47 (0.31–0.71)	NA	NA	0.68 (0.29–1.60)	0.68 (0.36–1.30)
Multivariate analysis								
Early therapy vs. delayed therapy	0.04 (0.01–0.28)	0.04 (0.01–0.19)	0.11 (0.04–0.33)	0.11 (0.06–0.22)	0.59 (0.40–0.89)	0.59 (0.42–0.85)	0.28 (0.18–0.45)	0.28 (0.19–0.41)
Baseline CD4 count (per 100 CD4 increment)	1.24 (1.00–1.54)	1.24 (1.13–1.36)	1.22 (1.02–1.47)	1.22 (1.13–1.33)	0.90 (0.75–1.08)	0.90 (0.70–1.17)	1.11 (0.96–1.28)	1.11 (0.97–1.26)
Baseline viral load (per unit log10 increment)	2.85 (1.51–5.41)	2.86 (1.72–4.75)	2.13 (1.30–3.50)	2.13 (1.42–3.21)	1.65 (1.24–2.20)	1.65 (1.31–2.08)	1.60 (1.21–2.11)	1.60 (1.14–2.25)
Male sex vs. female sex	0.73 (0.33–1.65)	0.73 (0.48–1.13)	1.00 (0.51–1.97)	1.00 (0.58–1.71)	1.46 (0.95–2.26)	1.46 (1.09–1.96)	1.18 (0.78–1.80)	1.18 (0.79–1.76)
Baseline condom use (100% vs. < 100%)	0.33 (0.12–0.91)	0.33 (0.24–0.45)	0.41 (0.16–1.08)	0.41 (0.29–0.59)	NA	NA	0.64 (0.27–1.52)	0.64 (0.35–1.17)

Note: NA = not applicable. Source: Authors' construction using the data from the original authors.

3.3 Circumcision

In the last decade, three studies (Auvert et al. 2005; Bailey et al. 2007; Gray et al. 2007) found that medical male circumcision is effective in reducing the risk of heterosexually acquired HIV infection in men by about 60 per cent. These three studies were so influential that WHO and UNAIDS recommended medical male circumcision as an efficacious intervention for the prevention of heterosexually acquired HIV infection in men (WHO and UNAIDS 2007).

The HPTN052 study did not control for the circumcision status of HIV-1-uninfected males, although it found a statistically significant imbalance in the proportion of circumcised men in the early therapy group and the delayed therapy group at baseline. Furthermore, 51 per cent of the total participants were men. As circumcision status may significantly affect the analysis in this study, we planned to control for male circumcision in our original analysis plan for the MEA. However, we were not able to conduct this analysis as the original authors declined to provide the data on male circumcision, given evidence of measurement error.

3.4 Prior HIV treatment through PMTCT

Patients with HIV-1 infection were only eligible for this study if their CD4 count was between 350 and 550 (at the time not yet eligible for ART, with 550 considered 'healthy') and they had received no previous ART. An exception was made for prior use of ART due to short-term use for the prevention of mother-to-child transmission (PMTCT) of HIV-1.

Among the HIV-1-infected participants, 27 per cent of participants in both study arms were women who reported prior ART use for PMTCT. Evidence suggests that women with prior exposure to ART through PMTCT, or women with ART interruption due to PMTCT, have poorer health outcomes once they begin lifetime ART treatment (Naidu et al. 2012).

Given this evidence, we conducted a subgroup analysis on women with prior ART treatment for PMTCT. We created two subgroups: one with HIV-1-infected women who have received prior ART for PMTCT (27% of HIV-1-infected women in the total group, or 235 women), and one with the remainder of participants with no prior exposure to ART (the remainder of the total group including 73% of HIV-1-infected women). Given that the sample size of participants with prior exposure to ART for PMTCT is relatively small, we did not run any analysis given severe lack of power. Our Table 8 presents the results for the subgroup of participants with no prior exposure.

The results for linked HIV-1 transmission and any transmission of HIV-1 are identical to those presented in Table 2 in the original paper, given that these outcomes did not originally include participants with prior exposure to ART. For these analyses, participants are censored when they become HIV infected (the outcome of interest). Women with prior exposure to ART are naturally excluded because they already have the outcome of interest (HIV-1 infection).

Conversely, the results presented in our Table 8 for clinical events and composite events are slightly different from those presented in the original paper, given that these

outcomes are for participants infected with HIV-1 at baseline. In fact, as in the original paper, these results show that even when restricting participants to those with no prior exposure to ART, early therapy has a protective effect against clinical events and composite events. For clinical events, the hazard ratio in the early therapy group is 0.60 (95% CI, 0.40 to 0.91), whereas for composite events the hazard ratio in the early therapy group is 0.31 (95% CI, 0.19 to 0.49).

We used the Kaplan–Meier method to produce our Figure 4 by restricting participants to those with no prior exposure to ART for PMTCT. We used the same methods as the original study to produce unadjusted survival curves for the two study arms. Figures 4A and 4B are the Kaplan–Meier estimates for the cumulative probabilities of partner-linked and any HIV-1 transmission in the early therapy and delayed therapy groups.

Panel 2, the subgroup with no prior exposure to ART for PMTCT, is identical to the figures in panel 1 (the original results) for partner-linked and any transmission of HIV-1, for the reasons discussed above. Figures 4C and 4D are the Kaplan–Meier estimates for the cumulative probabilities of clinical events and composite events in the early therapy group and the delayed therapy groups. Panel 2, the subgroup with no prior exposure to ART for PMTCT, is similar in shape to the figures in panel 1 (the original results).

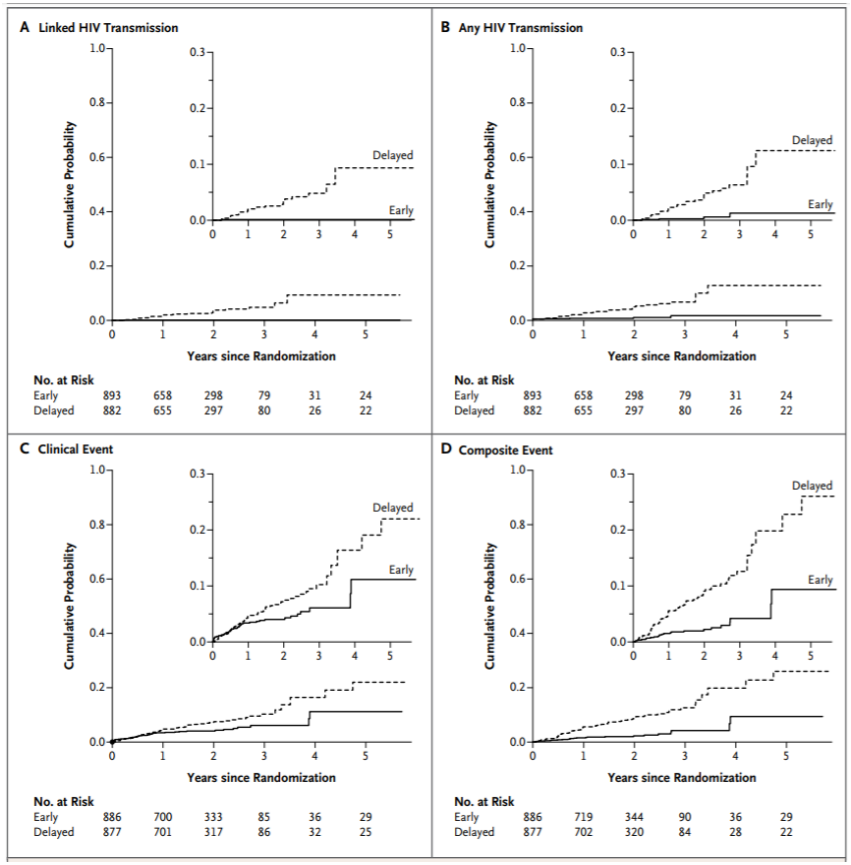
Table 8: Incidence of partner-linked and any HIV-1 transmission and clinical and composite events (sample with no prior ART use for PMTCT)

	Early therapy			Delayed therapy			
	Events	Person-year	Rate (95% CI)	Events	Person-year	Rate (95% CI)	Hazard or rate ratio (95% CI)
Linked transmission							
Total	1	1,585.3	0.1 (0.0–0.4)	27	1,567.3	1.7 (1.2–2.5)	0.04 (0.01–0.27)
1 year	1	819	0.1 (0.0–0.9)	16	813.3	2.0 (1.2–3.2)	0.06 (0.00–0.40)
2–3 years	0	686.5	0.0 (0.0–0.0)	9	682.8	1.3 (0.7–2.5)	0.00 (0.00–0.50)
> 3 years	0	79.9	0.0 (0.0–0.0)	2	71.2	2.8 (0.7–11.2)	0.00 (0.00–5.18)
Any transmission							
Total	4	1,585.3	0.3 (0.1–0.7)	35	1,567.3	2.2 (1.6–3.1)	0.11 (0.04–0.32)
1 year	2	819	0.2 (0.1–1.0)	18	813.3	2.2 (1.4–3.5)	0.11 (0.01–0.46)
2–3 years	2	686.5	0.3 (0.1–1.2)	14	682.8	2.1 (1.1–3.5)	0.14 (0.02–0.62)
> 3 years	0	79.9	0.0 (0.0–0.0)	3	71.2	4.2 (1.4–13.1)	0.00 (0.00–2.35)
Clinical events							
Total	37	1,432.1	2.6 (1.9–3.6)	61	1,417.7	4.3 (3.3–5.5)	0.60 (0.40–0.91)
1 year	26	719.6	3.6 (2.5–5.3)	37	718.1	5.2 (3.7–7.1)	0.76 (0.44–1.30)
2–3 years	10	638.9	1.6 (0.8–2.9)	19	626.5	3.0 (1.9–4.8)	0.51 (0.21–1.14)
> 3 years	1	73.6	1.4 (0.2–9.6)	5	73.1	6.8 (2.8–16.4)	0.21 (0.00–1.90)
Composite events							
Total	22	1,456.6	1.5 (0.9–2.3)	70	1,415.3	4.9 (3.9–6.3)	0.31 (0.19–0.49)
1 year	13	727.7	1.8 (1.0–3.1)	41	718.8	5.7 (4.2–7.7)	0.36 (0.18–0.69)
2–3 years	8	654.2	1.2 (0.6–2.4)	23	629.4	3.7 (2.4–5.5)	0.33 (0.13–0.76)
> 3 years	1	74.7	1.3 (0.2–9.5)	6	67.2	8.9 (4.0–19.9)	0.16 (0.00–1.37)

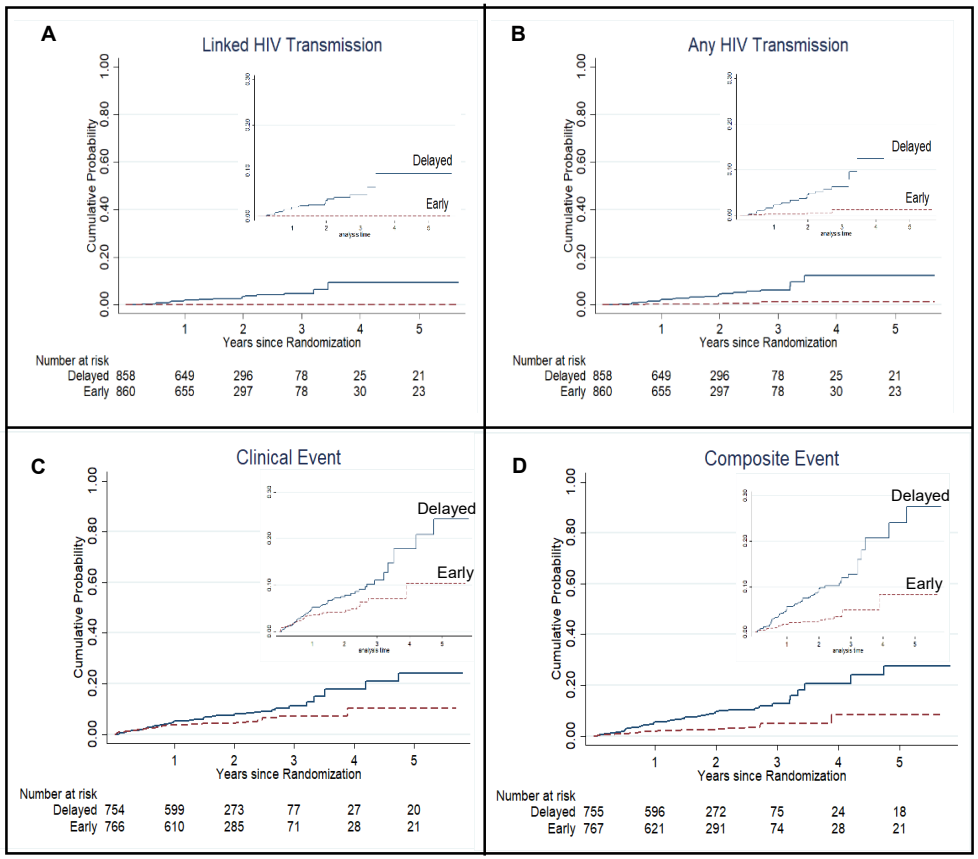
Source: Panel 1 (original results) from Cohen and colleagues (2011). Panel 2 (replication results) authors' construction using the data from the original authors.

Figure 4: Kaplan–Meier estimates for partner-linked and any HIV-1 transmission and for clinical and composite events (subgroup with no prior ART use for PMTCT)

Panel 1: Original results



Panel 2: Results for subgroup with no prior ART use for PMTCT



Source: Authors' construction using the data from the original authors.

3.5 Cox proportional hazards assumption

In the HPTN052 study, the authors used Cox regression analyses to estimate relative risk ratios. Cox analyses are often used to conduct survival-time analyses to estimate the length of time it takes for an event to occur. In this case, the events of interest are any transmission of HIV-1, partner-linked transmission of HIV-1, clinical events and composite events. However, the validity of the Cox model relies on whether all predictors satisfy the proportional hazards assumptions.

Violations of these assumptions can produce results that are not meaningful, indicating that a different estimation strategy would be more appropriate to estimate the effect of the intervention (Lin et al. 1993). In this case, the assumption of constant relative hazard might not hold true, given that treatment may lower transmission risk and that new HIV-1 infection may be more likely to result in transmission.

We used two different methods to test the Cox proportional hazards assumption: using Schoenfeld residuals and including time-dependent covariates in the model. We conducted these tests using key variables that apply to both HIV-1-infected and HIV-1-uninfected participants included in Table 1 on baseline characteristics, in the original study by Cohen and colleagues (2011).

Using Schoenfeld residuals tests whether there is independence between residuals and time. This test is analogous to testing whether the slope of scaled residuals on time is zero; a non-zero slope could indicate a violation of the proportional hazard assumption.

Table 9 shows the results of using Schoenfeld residuals to test for the different outcomes and the covariates used in the multivariate analysis, including age, sex, educational status, self-reported sexual behaviour and rate of condom use. As we can see, no p-values (prob > chi2) are less than 0.05. Thus, we fail to reject the null hypothesis that the slope is zero and conclude that the treatment status and the covariates meet the Cox proportional hazards assumption.

To further test the proportional hazards assumption, we included time-dependent covariates in the model. This test generates time-dependent covariates by creating interactions of the predictors and a function of survival time; any statistically significant ($p < 0.05$) results would not be proportional. Results are stratified by site, as in the original analysis. Tables 9–13 present these results for linked transmission, any transmission, clinical events and composite events. Results show that none of the time-dependent covariates are statistically significant, implying that the Cox proportional hazards assumption is met.

Table 9: Testing the assumptions of the Cox proportional hazards model

		Linked transmission				Any transmission				Clinical events				Composite events			
		rho	chi2	df	prob > chi2	rho	chi2	df	prob > chi2	rho	chi2	df	prob > chi2	rho	chi2	df	prob > chi2
Treatment		-0.19	1.04	1	0.31	0.03	0.03	1	0.87	-0.13	1.98	1	0.16	-0.01	0.01	1	0.91
Sex (men = 0, women = 1)		-0.01	0.00	1	0.94	0.09	0.28	1	0.60	0.07	0.55	1	0.46	0.06	0.36	1	0.55
Age group	18–25 years			1				1				1				1	
	26–40 years	0.28	1.71	1	0.19	0.10	0.28	1	0.60	0.12	1.47	1	0.23	0.04	0.19	1	0.66
	> 40 years	-0.12	0.38	1	0.54	-0.17	1.18	1	0.28	0.07	0.47	1	0.50	0.01	0.00	1	0.95
Education	No schooling			1				1				1				1	
	Primary schooling	-0.11	0.31	1	0.58	-0.14	0.73	1	0.39	-0.01	0.01	1	0.94	0.04	0.19	1	0.66
	Secondary schooling	-0.11	0.29	1	0.59	-0.20	1.50	1	0.22	0.10	1.15	1	0.28	0.14	1.98	1	0.16
	Post-secondary schooling	-0.01	0.00	1	0.96	-0.03	0.05	1	0.83	0.01	0.00	1	0.95	0.01	0.02	1	0.89
Marital status	Single			1				1				1				1	
	Married or living with partner	0.30	1.44	1	0.23	0.06	0.10	1	0.75	0.07	0.51	1	0.47	0.04	0.22	1	0.64
	Widowed, separated or divorced	0.24	0.00	1	1.00	0.05	0.00	1	1.00	0.04	0.00	1	1.00	0.05	0.00	1	1.00
Condom use in last week (no unprotected sex = 0, any unprotected sex = 1)		-0.02	0.01	1	0.92	0.04	0.07	1	0.80	0.01	0.02	1	0.88	-0.03	0.08	1	0.77
No. of sex partners in past 3 months	0–1			1				1				1				1	
	2–4	-0.26	1.92	1	0.17	0.00	0.00	1	0.98	0.08	0.68	1	0.41	0.16	2.59	1	0.11
	> 4	-0.15	0.00	1	1.00	0.02	0.00	1	1.00	-0.02	0.00	1	1.00	0.08	0.77	1	0.38
No. of sexual encounters in past week	0			1				1				1				1	
	1–2	-0.09	0.24	1	0.62	-0.20	1.57	1	0.21	0.08	0.70	1	0.40	0.07	0.47	1	0.49
	3–4	-0.01	0.00	1	0.96	-0.04	0.05	1	0.82	0.02	0.03	1	0.87	0.03	0.09	1	0.76
	> 4	0.08	0.16	1	0.69	-0.01	0.00	1	0.96	0.18	3.44	1	0.06	0.04	0.16	1	0.69
Global test			9.13	15	0.87		7.18	15	0.95		13.01	15	0.60		9.50	15	0.85

Note: We used Schoenfeld residuals to test the proportional hazards assumption along sex, age, education level, marital status and sexual activity.

Source: Authors' construction using the data from the original authors.

Blank cells denote the reference group for the categorial variable considered and automatically excluded from the regression by Stata®.

Table 10: Testing the assumptions of the Cox proportional hazards model: linked transmission

Linked transmission		_t	Coefficient	Standard error	z	P > z	[95% CI]	
main								
	Education	No schooling						
		Primary schooling	1.20	1.09	1.10	0.27	-0.93	3.33
		Secondarery schooling	1.00	1.11	0.90	0.37	-1.18	3.18
		Post-secondary schooling	1.01	1.31	0.77	0.44	-1.56	3.57
	Marital status	Single						
		Married or living with partner	-0.48	1.25	-0.39	0.70	-2.92	1.96
		Widowed, separated or divorced	-34.83	1.36E+08	0	1	-2.66E+08	2.66E+08
	No. of sex partners in past 3 months	0–1						
		2–4	0.74	0.68	1.08	0.28	-0.60	2.08
		> 4	-32.85	6.31E+07	0.00	1.00	-1.24E+08	1.24E+08
	No. of sexual encounters in past week	0						
		1–2	0.80	0.59	1.35	0.18	-0.36	1.97
		3–4	0.98	0.65	1.50	0.13	-0.30	2.25
		> 4	0.62	0.94	0.66	0.51	-1.23	2.46
tvc								
	Education	No schooling						
		Primary schooling	-0.65	1.46	-0.45	0.66	-3.50	2.21
		Secondary schooling	-0.76	1.49	-0.51	0.61	-3.68	2.16
		Post-secondary schooling	-0.54	1.76	-0.31	0.76	-3.98	2.90
	Marital status	Single						
		Married or living with partner	0.82	1.97	0.42	0.68	-3.03	4.68
		Widowed, separated or divorced	2.52	1.79E+08	0	1	-3.51E+08	3.51E+08
	No. of sex partners in past 3 months	0–1						
		2–4	-0.87	0.81	-1.07	0.29	-2.45	0.72
		> 4	0.00	(omitted)				
	No. of sexual encounters in past week	0						
		1–2	-0.61	0.78	-0.79	0.43	-2.15	0.92
		3–4	-0.31	0.86	-0.36	0.72	-1.99	1.37
		> 4	0.69	1.46	0.47	0.64	-2.18	3.55
				Likelihood-ratio test			LR chi2 (9)	3.11
							Prob > chi2	0.96

Note: We used time-dependent covariates to test the proportional hazards assumption along sex, age, education level, marital status and sexual activity. Time-dependent covariates are interacted with the log(time) in tvc equation.

Source: Authors' construction using the data from the original authors. Blank cells denote the reference group for the categorial variable considered and automatically excluded from the regression by Stata®.

Table 11: Testing the assumptions of the Cox proportional hazards model: any transmission

Any transmission								
		_t	Coefficient	Standard error	z	P > z	[95% CI]	
main								
	Education	No schooling						
		Primary schooling	0.97	0.93	1.04	0.30	-0.86	2.80
		Secondary schooling	0.77	0.95	0.81	0.42	-1.10	2.64
		Post-secondary schooling	0.44	1.16	0.38	0.70	-1.84	2.73
	Marital status	Single						
		Married or living with partner	-0.55	0.93	-0.59	0.56	-2.37	1.28
		Widowed, separated or divorced	-36.55	2.50E+08	0	1	-4.89E+08	4.89E+08
	No. of sex partners in past 3 months	0–1						
		2–4	1.04	0.52	2.00	0.05	0.02	2.07
		> 4	-35.03	1.97E+08	0.00	1.00	-3.86E+08	3.86E+08
	No. of sexual encounters in past week	0						
		1–2	0.05	0.45	0.12	0.91	-0.82	0.93
		3–4	0.25	0.50	0.49	0.62	-0.74	1.23
		> 4	0.52	0.63	0.82	0.41	-0.72	1.76
tvc								
	Education	No schooling						
		Primary schooling	-1.07	1.30	-0.82	0.41	-3.62	1.49
		Secondary schooling	-1.53	1.34	-1.14	0.25	-4.16	1.10
		Post-secondary schooling	-1.07	1.59	-0.67	0.50	-4.19	2.06
	Marital status	Single						
		Married or living with partner	-0.55	1.39	-0.40	0.69	-3.27	2.17
		Widowed, separated or divorced	0.45	3.48E+08	0	1	-6.82E+08	6.82E+08
	No. of sex partners in past 3 months	0–1						
		2–4	-0.16	0.66	-0.25	0.80	-1.46	1.13
		> 4	0.60	2.11E+08	0.00	1.00	-4.14E+08	4.14E+08
	No. of sexual encounters in past week	0						
		1–2	-0.82	0.62	-1.33	0.18	-2.03	0.39
		3–4	-0.52	0.68	-0.77	0.44	-1.86	0.82
		> 4	0.03	0.93	0.03	0.98	-1.80	1.85
				Likelihood-ratio test			LR chi2 (10)	4.48
							Prob > chi2	0.92

Note: We used time-dependent covariates to test the proportional hazards assumption along sex, age, education level, marital status and sexual activity. Time-dependent covariates are interacted with the log(time) in tvc equation.

Source: Authors' construction using the data from the original author. Blank cells denote the reference group for the categorial variable considered and automatically excluded from the regression by Stata®.

Table 12: Testing the assumptions of the Cox proportional hazards model: clinical events

Clinical events		_t	Coefficient	Standard error	z	P > z	[95% CI]	
main								
	Education	No schooling						
		Primary schooling	-0.10	0.35	-0.30	0.76	-0.78	0.58
		Secondary schooling	-0.05	0.36	-0.15	0.88	-0.75	0.65
		Post-secondary schooling	-0.42	0.50	-0.84	0.40	-1.41	0.56
	Marital status	Single						
		Married or living with partner	1.48	1.27	1.16	0.25	-1.01	3.97
		Widowed, separated or divorced	-33.48	7.17E+07	0	1	-1.41E+08	1.41E+08
	No. of sex partners in past 3 months	0–1						
		2–4	-0.53	0.77	-0.69	0.49	-2.04	0.98
		> 4	-34.77	6.64E+07	0.00	1.00	-1.30E+08	1.30E+08
	No. of sexual encounters in past week	0						
		1–2	-0.18	0.25	-0.74	0.46	-0.66	0.30
		3–4	-0.23	0.36	-0.64	0.52	-0.93	0.47
		> 4	-0.49	0.65	-0.76	0.45	-1.76	0.78
tvc								
	Education	No schooling						
		Primary schooling	-0.02	0.25	-0.10	0.92	-0.51	0.46
		Secondary schooling	0.30	0.28	1.06	0.29	-0.25	0.85
		Post-secondary schooling	0.24	0.42	0.57	0.57	-0.58	1.05
	Marital status	Single						
		Married or living with partner	0.87	0.75	1.17	0.24	-0.59	2.33
		Widowed, separated or divorced	0.47	5.17E+07	0	1	-1.01E+08	1.01E+08
	No. of sex partners in past 3 months	0–1						
		2–4	0.94	0.85	1.11	0.27	-0.73	2.61
		> 4	0.07	5.65E+07	0.00	1.00	-1.11E+08	1.11E+08
	No. of sexual encounters in past week	0						
		1–2	0.09	0.19	0.48	0.63	-0.28	0.47
		3–4	-0.06	0.26	-0.25	0.80	-0.56	0.44
		> 4	1.17	0.70	1.66	0.10	-0.21	2.55
				Likelihood-ratio test			LR chi2 (12)	9.57
							Prob > chi2	0.65

Note: We used time-dependent covariates to test the proportional hazards assumption along sex, age, education level, marital status and sexual activity. Time-dependent covariates are interacted with the log(time) in tvc equation.

Source: Authors' construction using the data from the original authors.

Blank cells denote the reference group for the categorial variable considered and automatically excluded from the regression by Stata®.

Table 13: Testing the assumptions of the Cox proportional hazards model: composite events

Composite events		_t	Coefficient	Standard error	z	P > z	[95% CI]	
main								
	Education	No schooling						
		Primary schooling	0.40	0.43	0.94	0.35	-0.44	1.23
		Secondary schooling	0.44	0.44	1.00	0.32	-0.42	1.30
		Post-secondary schooling	-0.31	0.63	-0.50	0.62	-1.54	0.91
	Marital status	Single						
		Married or living with partner	0.24	0.77	0.32	0.75	-1.26	1.75
		Widowed, separated or divorced	-33.23	3.22E+07	0	1	-6.32E+07	6.32E+07
	No. of sex partners in past 3 months	0–1						
		2–4	-1.68	1.28	-1.31	0.19	-4.20	0.84
		> 4	0.44	2.14	0.20	0.84	-3.76	4.63
	No. of sexual encounters in past week	0						
		1–2	0.02	0.26	0.08	0.93	-0.48	0.52
		3–4	-0.06	0.33	-0.19	0.85	-0.72	0.59
		> 4	0.28	0.42	0.68	0.50	-0.54	1.11
tvc								
	Education	No schooling						
		Primary schooling	0.31	0.36	0.88	0.38	-0.39	1.01
		Secondary schooling	0.70	0.39	1.79	0.07	-0.06	1.46
		Post-secondary schooling	0.48	0.56	0.86	0.39	-0.61	1.57
	Marital status	Single						
		Married or living with partner	0.25	0.60	0.41	0.68	-0.93	1.43
		Widowed, separated or divorced	-0.11	2.49E+07	0	1	-4.89E+07	4.89E+07
	No. of sex partners in past 3 months	0–1						
		2–4	2.10	1.36	1.54	0.12	-0.57	4.78
		> 4	2.08	2.78	0.75	0.45	-3.36	7.52
	No. of sexual encounters in past week	0						
		1–2	0.21	0.24	0.87	0.38	-0.26	0.69
		3–4	0.01	0.31	0.05	0.96	-0.60	0.63
		> 4	0.25	0.43	0.58	0.56	-0.59	1.08
				Likelihood-ratio test			LR chi2 (10)	10.77
							Prob > chi2	0.38

Note: We used time-dependent covariates to test the proportional hazards assumption along sex, age, education level, marital status and sexual activity. Time-dependent covariates are interacted with the log(time) in tvc equation.

Source: Authors' construction using the data from the original authors.

Blank cells denote the reference group for the categorial variable considered and automatically excluded from the regression by Stata®.

3.6 Understanding how the intervention works

ART is effective in treating HIV-1 infection only when there is a significant reduction of viral load. Thus, early initiation of ART could be effective in reducing the likelihood of HIV-1 transmission due to a reduced viral load. The original authors did not explicitly test whether, over time, the viral load is significantly lower in the early therapy group compared with the delayed therapy group. This is an important outcome to measure for future studies.

Furthermore, the reduction of viral load requires a high level of adherence to ART. Good adherence to ART is a strong predictor of positive health and treatment outcomes for HIV-infected patients (Ross-Degnan et al. 2010). In our replication, we planned to assess whether the effect of early initiation of ART on rates of sexual transmission of HIV-1 varies by the level of adherence to ART. However, we were not able to conduct this analysis as the original authors declined to provide us with data of the level of adherence to ART. The main reason cited by the original authors is that they see nothing to replicate.[9]

4. Discussion and conclusion

4.1 Discussion

The results of this replication study have several important implications. The pure replication suggests that Figure 2 in the original paper may have been produced with a different dataset from the one provided to us. The research team gave instructions on how to deal with the missing data that caused the discrepancies during replication (duration values for 57 HIV-1-uninfected participants and 9 HIV-1-infected participants); however, these instructions did not solve the problem.

This is a major difference that requires further investigation from the original authors. If this error is confirmed by the original authors, an 'errata' should be submitted to the *New England Journal of Medicine*. Other than this major difference in Figure 2 of the original paper, in general the main results reported in the original paper do not suffer from any errors that might come from different sources, such as construction of variables, data cleaning and codes used to obtain findings.

Thus, other than for Figure 2, we can confirm that the data and methods described by Cohen and colleagues (2011) are those used to produce the main findings reported in the original paper.

In the MEA, we separated the total group into two subgroups, one with the participants from African nations only and another with the participants from non-African nations only. Our results from the subgroup of participants from African nations only show that early initiation of ART is effective, as compared with delayed therapy.

[9] In order to supplement this analysis because of the lack of data on ART adherence, and to learn about the pathway from intervention to impact, we wished to test whether the early initiation of ART led to a change in CD4 levels and viral loads. However, the original authors only provided the baseline data on CD4 levels and viral loads. We were not able to access the endline data for these two variables to assess any changes due to the early initiation of ART.

The effect size is similar to what was found in the original paper. This shows that in regions such as Sub-Saharan Africa with a high average viral load level prior to ART initiation, early initiation is still very effective in reducing HIV-1 transmission. When we consider only the participants from non-African nations, we find no statistically significant impact of early initiation of ART on reduction in HIV-1 transmission, which we attribute to a lack of statistical power due to reduced sample size.

Furthermore, we clustered standard errors by site to consider the possibility of lack of independence within sites. This resulted in standard errors with narrowed confidence intervals, therefore increasing the significance level of the estimates. This result indicates that there could be a very low degree of intra-group correlation.

We were unable to control for male circumcision because the original authors declined to provide us with the data on male circumcision, citing that these data suffer from measurement error. This is unfortunate for this replication, because public health programming has been expanded through eastern and southern Africa to introduce medical male circumcision. Controlling for this could have an impact on the efficacy of early initiation of ART.

In addition, the original authors declined to provide the data on ART adherence, arguing that there was nothing to replicate. This data would have helped us to assess the level of ART adherence needed to see an impact from early initiation of ART.

Finally, we assessed the Cox proportional hazards assumption. We found that the Cox proportional hazards assumption is met for all outcomes and covariates used in the analyses. Thus, the results found in the original paper and in our replication are valid and do not suffer from the violation of the Cox proportional hazards assumption.

4.2 Conclusion

In this paper, we presented a replication study of *Prevention of HIV-1 infection with early antiretroviral therapy* (Cohen et al. 2011), using the data provided to us by the original authors. We first conducted a pure replication, using the same epidemiological methods as the original authors. In general – except for Figure 2 in the original paper, where we found a major difference with our replication – the pure replication confirmed the main findings of the original paper.

Second, in the measurement and estimation analysis, we conducted several subgroup analyses and robustness checks. In the subgroup analysis on participants from African nations, we found that early initiation of ART still reduced rates of sexual transmission of HIV-1 and clinical events when considering the participants from African nations only. However, due to the lack of statistical power given the reduced sample size, there are no conclusive results for the subgroup of participants from non-African nations only.

When clustering the standard errors by site, we found the same effect size for hazard ratios for multiple outcomes. This improved the statistical significance of the results given the narrower confidence intervals. We were not able to control for male circumcision or study the relationship between ART adherence and early ART initiation because the original authors declined to share the relevant data. Finally, we assessed the Cox proportional hazards assumption using two methods: examining time-dependent

covariates and using Schoenfeld residuals. We found that the Cox proportional hazards assumption was met.

The results of this replication confirm the analysis in the original HPTN052 study and in the recent follow-up study (Cohen et al. 2016) to show positive impacts of early initiation of ART in dramatically reducing HIV-1 transmission among serodiscordant couples. Furthermore, an additional study entitled *Partners of people on ART – a new evaluation of the risks (PARTNER)* showed that viral suppression (< 200 copies per millilitre) prevented sexual transmission of HIV (Rodger et al. 2016).

With the evidence confirmed through this replication, we find that early initiation of ART can be an effective strategy in reducing HIV-1 transmission among serodiscordant couples in clinical trials at a small scale. Four studies over the last seven to eight years have examined whether this efficacy can be observed at the population level or at a larger level.

Generally, early universal HIV testing and treatment has not resulted in a significantly lower incidence of HIV infection compared with standard care, mainly due to poor linkage in care. Thus, future research around the early initiation of ART should focus on how to improve the linkage to care for HIV-1-infected patients – from barriers at the individual level right up to the health systems level. This research will inform future programmatic design aiming to achieve a reduction of HIV transmission at the population level through early initiation of ART.

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