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Assessing the Effect of HIV Counseling and Testing on HIV Acquisition among South African Youth

Nora E Rosenberg, PhD^{1,2}, Daniel Westreich, PhD^{1,3,4}, Till Bärnighausen, MD ScD^{2,5}, William C. Miller, MD PhD^{1,6}, Frieda Behets, PhD^{1,6}, Suzanne Maman, PhD⁷, Marie-Louise Newell, PhD^{2,8}, and Audrey Pettifor, PhD¹

¹Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, USA

²Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Mtubatuba, South Africa

³Department of Obstetrics and Gynecology, Duke University, Durham, North Carolina, USA

⁴Global Health Institute, Duke University, Durham, Duke University, North Carolina, USA

⁵Department of Global Health and Population, Harvard School of Public Health, Boston, Massachusetts, USA

⁶Department of Medicine, School of Medicine, University of North Carolina at Chapel Hill, USA

⁷Department of Health Behavior and Health Education, University of North Carolina at Chapel Hill, USA

⁸Academic Unit of Human Development and Health, University of Southampton, Southampton UK

Introduction

Youth aged 15–24 years in sub-Saharan Africa are at high risk for HIV acquisition [1]. In South Africa, the country with the world's largest burden of HIV infection, an estimated 21% of girls and 5% of boys have acquired HIV by the time they are 24 years old [2,3]. Thus, youth in this age range urgently need effective HIV prevention interventions to slow HIV incidence.

Although HIV counseling and testing (HCT) is designed to target HIV risk behaviors and has been widely implemented throughout the region, the impact of HCT on HIV acquisition has never been studied among youth in sub-Saharan Africa. Among HIV-uninfected adults living in sub-Saharan Africa, research with HIV endpoints suggests HCT leads to stable or modestly elevated HIV acquisition rates [4–7], a finding that may be due to behavioral disinhibition following HCT [8], confounding or other biases, or spurious associations. The

Corresponding Author: Nora E. Rosenberg, PhD, University of North Carolina Project, Tidziwe Center, Private Bag A-104, Lilongwe, Malawi, Phone: +265 99 109 0676, Nora_Rosenberg@unc.edu.

Conflicts of interest

There are no conflicts of interest.

Duplicate publication

Results have not been published previously, but will be presented at the Conference on Retroviruses and Opportunistic Infections in March 2013 as a research poster.

implications of these findings are unclear for youth, who are behaviorally and socially different from adults [9] and more likely to be HIV-uninfected, especially at younger ages. Many youth have not yet experienced sexual debut, and early behavioral interventions, including HCT, may be more effective at establishing or reinforcing safer sexual behavior during this formative period [10]. Additionally, sexually active youth are not typically in marital or cohabitating partnerships [11], and condom use may be easier to negotiate in these less established partnerships. A cluster randomized trial, Project Accept, assessed the impact of intensive community-based HCT versus standard clinic-based HCT on HIV incidence among persons 18–24 years [12] at the community level and found no significant reduction in HIV incidence [13]. However, the impact of experiencing HCT versus not at the individual level has not been assessed among youth.

We assessed HIV acquisition among youth 15–24 years comparing those who had not been exposed to HCT to those who had been exposed to HCT using data from a household and HIV surveillance conducted by the Africa Centre for Health and Population Studies in South Africa [14].

Methods

Setting

The study was conducted in Hlabisa, a rural sub-district in KwaZulu-Natal. Overall HIV prevalence has been estimated at 23%, and HIV incidence at 3.4 per 100 person-years [15, 16]. By 2005, HCT was available in all primary health centers in the sub-district to support a decentralized HIV care and treatment program [17]. From 2005–2010, HCT was provided to persons presenting voluntarily and offered to patients presenting for antenatal care, sexually transmitted infections, and tuberculosis with high uptake [18]. Starting in mid-2010, HCT was expanded and offered to all patients. Since 2008, home- and mobile-HCT have also been available in some parts of the sub-district [19]. All clinic-, home-, and mobile-HCT services are counselor-delivered and incorporate education about how HIV is transmitted and counseling on sexual behavior risk reduction. All clients are provided with same-day results. The impact of these HCT services on HIV acquisition among youth was assessed using data sources described below.

Data Sources and Study Population

Within an enumerated part of the Hlabisa sub-district, two data sources collected within the same catchment area can be linked together: a household surveillance and an HIV and health survey. The household surveillance contains demographic and household characteristics of residents and non-residents of any age. The household surveillance is collected biannually by trained interviewers conducting in-person interviews with a household proxy. The HIV and health survey includes self-reported sexual behavior and HCT information, as well as anonymised laboratory-based HIV results. This survey is offered annually to all residents 15 years and older and 12.5% of non-residents. Data are collected by trained field-workers of the same gender. All questions are administered in isiZulu.

We conducted a cohort study using data collected from these two sources. For this analysis, in each year from 2006 to 2011, one household surveillance record and one HIV survey record were merged together using a unique identifier. These annual records were then combined over time so an individual's HCT history, covariates, and HIV status could be assessed in a time-varying manner.

Participants were eligible for inclusion in the analysis if they were 15–24 years at any point from 2006–2010 with at least two records in the HIV survey. Participants had to have sufficient self-reported information to determine whether and when they received HCT, have been HIV-uninfected at the origin, and have at least one year of follow-up.

Exposure, Outcome, and Covariates

The primary factor of interest was if and when a participant became aware of his or her HIV status from HCT. This was assessed based on a participant's response to a question from the HIV and health survey: "Do you know your HIV status from previous HIV testing?" The time origin for this analysis was the midpoint between the first two responses to this question. Using the midpoint allowed for an estimate of when HCT had occurred, the natural time origin for this research question. Participants who responded "no" at their first time point and "yes" at their second time point initially were considered "HCT-exposed." Participants who responded "no" at both their first and second time points initially were considered "HCT-unexposed." Participants who did not have at least two responses and those who responded "yes" at their first time point were excluded. Persons with two initial "yes" responses were excluded because there was missing person-time between HCT occurrence and the initiation of follow-up. Because of this missing person-time, we could not calculate a meaningful origin, determine what covariate values would have been at that origin, assess how long after the origin an event had occurred, or compare these observations to others experiencing the same amount of person-time [20].

After the origin, exposure to HCT was treated as time-varying. Participants who were HCT-exposed at the origin had all of their person-time characterized as HCT-exposed. Participants who were HCT-unexposed at the origin and all subsequent time points had all of their person-time characterized as HCT-unexposed. Participants who were initially HCT-unexposed, but later HCT-exposed had their person time split: the first portion time was characterized as HCT-unexposed and the second portion, after HCT occurred, as HCT-exposed.

The primary outcome of interest was HIV seroconversion, obtained from the HIV and health survey. For consenting participants, blood was obtained via finger prick and prepared into dried blood spots. A serial HIV testing algorithm with two ELISAs was performed in a laboratory: Vironostika HIV-1/HIV-2 Microelisa System (Biomérieux, Durham, NC, USA), followed by Wellcozyme HIV 1+2 GACELISA (Murex Diagnostics, Benelux B.V., Breukelen, The Netherlands) [21]. In the initial rounds of the HIV and health survey, participants could retrieve their HIV test results. However, due to extremely low uptake this practice was ceased, a decision that received ethical approval. Instead, all participants were encouraged to seek HCT at local health centers described above.

The laboratory-based HIV test results were used to determine the end of follow-up. The timing of seroconversion was the midpoint between the last HIV-negative result and the first HIV-positive result minus thirty days. Thus, if a change in exposure and change in outcome occurred in the same survey round, we presume the outcome preceded the exposure. Non-seroconverters were censored at the time of their last HIV-negative or indeterminate HIV test minus thirty days. Thirty days were subtracted to allow for a window period between HIV acquisition and detection through antibodies [21]. Persons who refused to provide blood for the HIV survey after their last HIV-negative test were characterized as “refusals” and censored.

Household-level characteristics, such as distance to the nearest primary health center, and individual demographic traits came from the household surveillance. Self-reported sexual behavior came from the HIV and health survey. Covariates were treated as time-varying, when appropriate.

Statistical Analyses

A directed acyclic graph was used to identify the covariates used in this analysis [22]. The covariates were gender, age, year of first HCT report, distance to the nearest primary health center, education, ever pregnant, fatherhood status, whether sexual debut had occurred, number of sex partners in the last year, and condom use at last sex. For some participants (21%), information was missing for at least one of the following covariates: education, pregnancy, fatherhood, sexual debut, number of sex partners, and condom use. Multiple imputation using Markov Chain Monte Carlo simulation was used to impute missing values of these covariates separately for the HCT-exposed and HCT-unexposed participants [23]. Five complete imputed data sets were generated using PROC MI and results were combined using PROC MIANALYZE in SAS 9.3 [24].

Descriptive statistics were calculated based on HCT status at the origin (Table 1). HIV incidence rates were calculated within strata of time-varying variables (Table 2). Cox proportional hazard models were used to estimate the association of HCT with time to HIV acquisition. We conducted two main hazard analyses: unweighted (i.e. crude) and inverse probability of exposure and censoring weighted (i.e. a marginal structural model) (Table 3) [25]; the latter of these can appropriately address time-varying confounding. In the marginal structural model, inverse probability of exposure and censoring weights were created separately based on time-fixed and time-varying covariates and then multiplied to produce final weights. Final weights were stabilized with time-fixed variables, and censored at the 1st and 99th percentiles to mitigate the influence of extreme weights [26]. Weights were distributed appropriately with a mean of 1.02 (standard deviation=0.34) and a median of 0.98 (range 0.10 – 7.78). The hazard of HIV acquisition by HCT status was estimated in a dataset with one observation per person quarter (i.e. three-month increment) using discrete time hazard models. These hazard models were estimated with pooled logistic regression using robust variance estimators and exchangeable correlation matrices. Time of HCT was used as the time origin [27].

Sensitivity Analyses

We conducted additional analyses to explore whether results were sensitive to model structure and assumptions. We implemented a marginal structural model with only inverse probability of exposure weights, but no censoring weights, to assess whether exposure or censoring weights were driving the difference between the unweighted and weighted effects. Next, we implemented a complete case analysis (i.e. an analysis among individuals with no missing data) to assess the extent to which the imputation assumptions could be driving the results. Finally, we implemented a model using covariate adjustment, rather than weights because such methods are more familiar. However, in the presence of time-varying confounding affected by prior exposure, covariate-adjusted Cox models can result in biased estimates of effect [25, 26].

Statistical analyses were implemented using SAS 9.3.

Ethics Approval

Permission for collecting the household surveillance and HIV and health survey data was obtained from the University of KwaZulu-Natal research ethics committee, and renewed annually. The current analysis was approved by the Public Health-Nursing Institutional Review Board at the University of North Carolina, Chapel Hill.

Results

Study Population

Overall, 18,383 persons 15–24 years were enumerated in the catchment area in at least two surveillance rounds from 2006–2010 (Figure 1). Youth who were HIV-infected before the origin (N=1054, 6%) were excluded as were youth who reported knowing their HIV status at their first HCT report (N=3985, 22%), since we could not estimate the origin. Persons with missing HCT status, HIV status, or both were also excluded. Most of these excluded youth were migrants enumerated as household members but not residing in the catchment area (N=6013, 33%). Others resided in the catchment area but had insufficient information to classify their exposure (HCT), outcome (HIV status), or both (N=3372, 18%). The study sample included the remaining youth (N=3959, 22%). Of these 1167 (29%) were initially HCT-exposed and 2792 (71%) initially HCT-unexposed. Of the persons who were initially HCT-unexposed, 38% became HCT-exposed during follow-up (N=1064) and the rest remained HCT-unexposed (N=1728). Among persons excluded for having missing information, some had sufficient HCT information for initial classification (N=1611, 48%). Of these excluded persons, the initial prevalence of HCT exposure was comparable (25%) to the initial prevalence of HCT exposure among included youth (29%) and covariate distributions were similar.

Population Characteristics

The study population was 51% male and 49% female with a median age of 17 (interquartile range: 16–20) (Table 1). The minority of women (17%) reported ever having been pregnant and few men (5%) reported ever having fathered a child. Initially, one third of participants reported sexual debut (34%) and 1 sex partners in the last year (32%), and 4% reported 2

partners in the last year. Of those who were sexually active, 43% reported condom use at last sex. Persons initially HCT-exposed were more likely to be female (59% versus 45%), sexually experienced (47% versus 29%), and previously pregnant (24% versus 14%) than those who were HCT-unexposed.

Main Analyses

Youth experienced 248 seroconversions over 8536 person-years of follow-up, an incidence rate of 2.91 per 100 person-years [95% confidence interval (CI): 2.56, 3.28]. In periods after HCT exposure, participants experienced 117 HIV events over 3834 person-years (HIV incidence rate: 3.05 per 100 person-years). In periods of HCT non-exposure, participants experienced 131 HIV events over 4702 person-years (HIV incidence rate: 2.79 per 100 person-years) (Table 2).

In unweighted Cox analysis, comparing HCT-exposed persons to HCT-unexposed persons, the hazard of HIV acquisition was 1.02 (95% CI: 0.79, 1.31) (Table 3, Figure 2). However, in the marginal structural model with inverse probability of exposure and censoring weights, the hazard of HIV acquisition was 0.59 (95% CI: 0.45, 0.78) (Table 3). Most of the change in estimate was attributed to exposure weighting for gender, sexual debut, and pregnancy. Hazard ratios were similar in the first 1.5 years after HCT (HR: 0.65 (95% CI: 0.40, 1.05) as in the next three years after HCT (HR: 0.57, 95% CI: 0.40, 0.79), suggesting durability. The effect was similar among men (HR: 0.66, 95% CI: 0.37, 1.38) and women (HR: 0.57, 95% CI: 0.41, 0.78), as well as between those <20 years (HR: 0.59, 95% CI: 0.43, 0.82) and those who were ≥ 20 years (HR: 0.56, 95% CI: 0.31, 0.97).

Sensitivity Analyses

In a marginal structural model with inverse probability of exposure weights, but no censoring weights, the hazard ratio was essentially identical to the main effect: 0.59 (95% CI: 0.44, 0.78), suggesting confounding, not refusal, was driving the difference between the unweighted and weighted effects (Table 3). In a marginal structural model without imputed covariates (i.e. a complete case analysis), the hazard ratio was similar, but estimated less precisely (HR: 0.64, 95% CI: 0.46, 0.89), suggesting the imputation model was not driving the results. In the covariate-adjusted model the hazard ratio was 0.65 (95% CI: 0.50, 0.86). The similarity between time-varying adjusted model and the marginal structural model suggests most of the confounding was simple time-varying confounding, not time-varying confounding from covariates being affected by prior exposure.

Discussion

We observed that youth in this high prevalence setting experienced a 41% reduction in the hazard of HIV acquisition following HCT, an effect sustained for 4.5 years. Youth who had experienced HCT were more likely to be female, pregnant, and to have experienced sexual debut. In short, the HCT-exposed youth were at greater risk for HIV acquisition. After accounting for these risk factors in longitudinal multivariable analyses, HCT was associated with lower HIV incidence.

In contrast, Project Accept, a study assessing community HCT compared to clinic HCT had no effect on HIV acquisition among persons 18–24 [13]. The difference between our results and Project Accept results may be explained by the differences in study design. Our study compared any HCT versus no HCT, whereas Project Accept compared community HCT to clinic HCT. Additionally, we measured HIV acquisition at the individual level, whereas Project Accept measured HIV incidence at the community level.

HCT may affect youth differently than adults. Among adults, HCT appears to have no effect or a small harmful effect on HIV acquisition [4–7]. The differential effects between youth and adults may be related to differences in life stages. Youth are still in a formative period with recent or no sexual debut, and may be better able to adopt counseling messages than adults, who have formed behavioral habits [10]. Additionally, in this setting, youth are primarily in non marital, non-cohabiting partnerships [11]. HCT may more readily facilitate protective sexual behaviors in these less stable partnerships [28].

Understanding the mechanism underlying the effect is a key question for future investigation. Changes in sexual behavior following HCT are one possible explanation as those in the catchment area who are aware of their HIV status are more likely to report condom use than those who are unaware [29]. Another potential explanation is that youth who sought HCT and knew they were HIV-uninfected were more likely to select other HIV-uninfected partners, though the prevalence and effect of sero-sorting in the African context is poorly understood. HCT referral to medical male circumcision, a prevention intervention for HIV-uninfected males, is unlikely to explain the effect, as it was not available until the end of the study period with low coverage.

Expanding age-appropriate access to HCT among youth could have important public health benefits. South Africa's recent decision to provide HCT in secondary schools is an important step towards greater access. However, questions about optimal timing and delivery modalities remain. South African youth often report stigmatizing care-seeking environments, and assessing whether youth-oriented HCT models improve service uptake and effectiveness in community-, clinic-, and school-based settings is an area for future investigation [9].

The benefits of HCT will likely be enhanced by additional prevention interventions. In this analysis, HIV-uninfected youth who received HCT still experienced a high HIV incidence rate (3 per 100 person-years), underscoring the importance of combination prevention. For HIV-uninfected youth, HCT can be an entry-point for medical male circumcision among young men and pre-exposure prophylaxis for high risk young men and women [30]. For HIV-infected youth, early HCT is necessary for early antiretroviral therapy for “treatment as prevention [31].” Developing appropriate linkages from HCT to these biomedical services for both HIV-infected and HIV-uninfected youth is a priority.

Large groups of youth were excluded or lost from this analysis, raising concerns about selection bias and non-generalizability. First, many persons who were HCT-exposed at the time of first report were excluded because it was not possible to estimate the time of HCT exposure or covariate values at that time. Exclusion of this high risk group could have made

HCT appear more protective than it truly was. Additionally, we excluded persons with insufficient HCT information, HIV information, or both. About two thirds (64%) of these persons were nonresidents, typically persons residing outside of the catchment area for work. In contrast, only 4% of youth in the analysis were non-residents, suggesting findings generalize best to residents. Of the remaining excluded youth, those with sufficient HCT information for initial classification had a comparable exposure and covariate distribution to the included youth, suggesting the excluded youth may not have been different from the included youth.

We did not have a perfect measure of HCT. We wanted to explore whether the frequency of HCT had an impact on HIV incidence, but were only able to assess first HCT, due to the phrasing of the question. Additionally, assessment of HCT was based on self-report, with the potential for misreporting. One possible sign of misreporting was that some youth reported HCT, even though they had not reported sexual debut. However, HCT in non-sexually active persons is expected when HCT is routinely offered, such as clinical settings with opt-out HCT. In spite of possible misreporting, trends in the HCT data are consistent with observed trends in the catchment area: females were more likely to report HCT than males, pregnant females were more likely to report HCT than non-pregnant females, and increases in age and calendar year were associated with increases in HCT. These associations are consistent with expectation and lend credibility to the exposure assessment.

This analysis may not have fully accounted for all factors influencing the effect of HCT on HIV acquisition. Youth who sought HCT may have had unmeasured traits that made them less risky than those who did not seek HCT. Additionally, some sexual behaviors, such as sexual debut, may have been under-reported due to social desirability, a likely phenomenon as many HIV acquisition events (77/248) occurred among persons who reported no sexual behavior. An alternative explanation for acquisition among youth who did not report debut is sexual abuse. In South Africa, boys 15–26 frequently report perpetrating rape [31] and school-age boys and girls report being victims of forced or coerced sex [33], events that may not have been reported in questions about debut and partnerships.

Given these potential sources of bias, replication of these results is warranted. In light of the rapid scale-up of HCT in the region and the unethical nature of withholding HCT, this question must be studied in non-randomized settings.

HCT is a necessary first step for reducing HIV transmission through linkage of HIV-infected persons to treatment. Based on our observations, HCT appears effective at reducing HIV acquisition among HIV-uninfected youth, even in the absence of biomedical prevention. These findings provide support to South Africa's recent decision to implement HCT in secondary schools [34], and suggest HCT may contribute to slowing HIV acquisition among this at-risk population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

NER conceptualized the study under the guidance of all co-authors. NER conducted analyses with guidance from DW, AEP, WCM, TB, and M-LN. M-LN and TB are investigators on the demographic and HIV surveillance and oversee data collection. NER drafted the initial manuscript and revisions were made by all co-authors. All co-authors approved the final draft.

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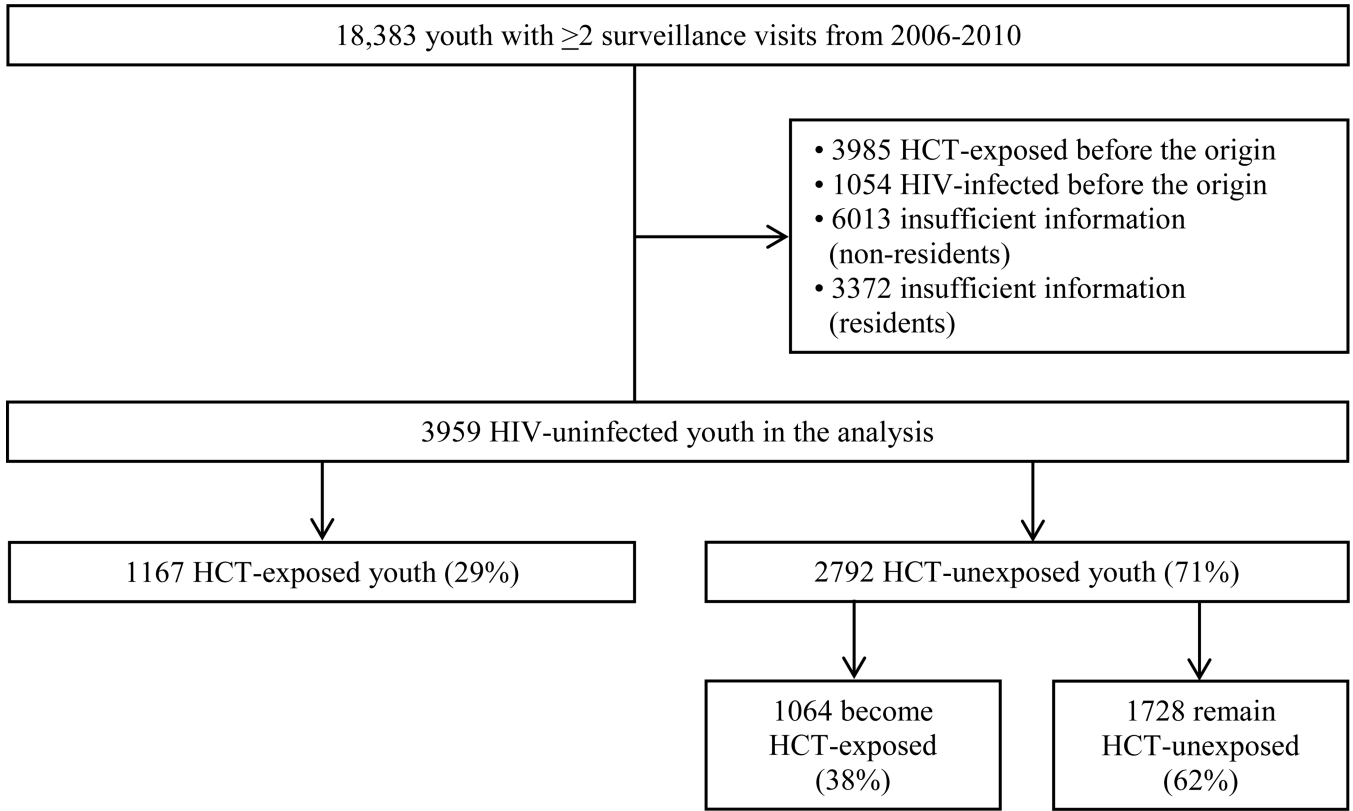


Figure 1. Study Population

Figure 1 illustrates the number of youth 15–24 in the catchment area with at least two surveillance time points from 2006–2010. It shows the proportion included and excluded from the analysis, and the proportion who experienced HCT initially and over time.

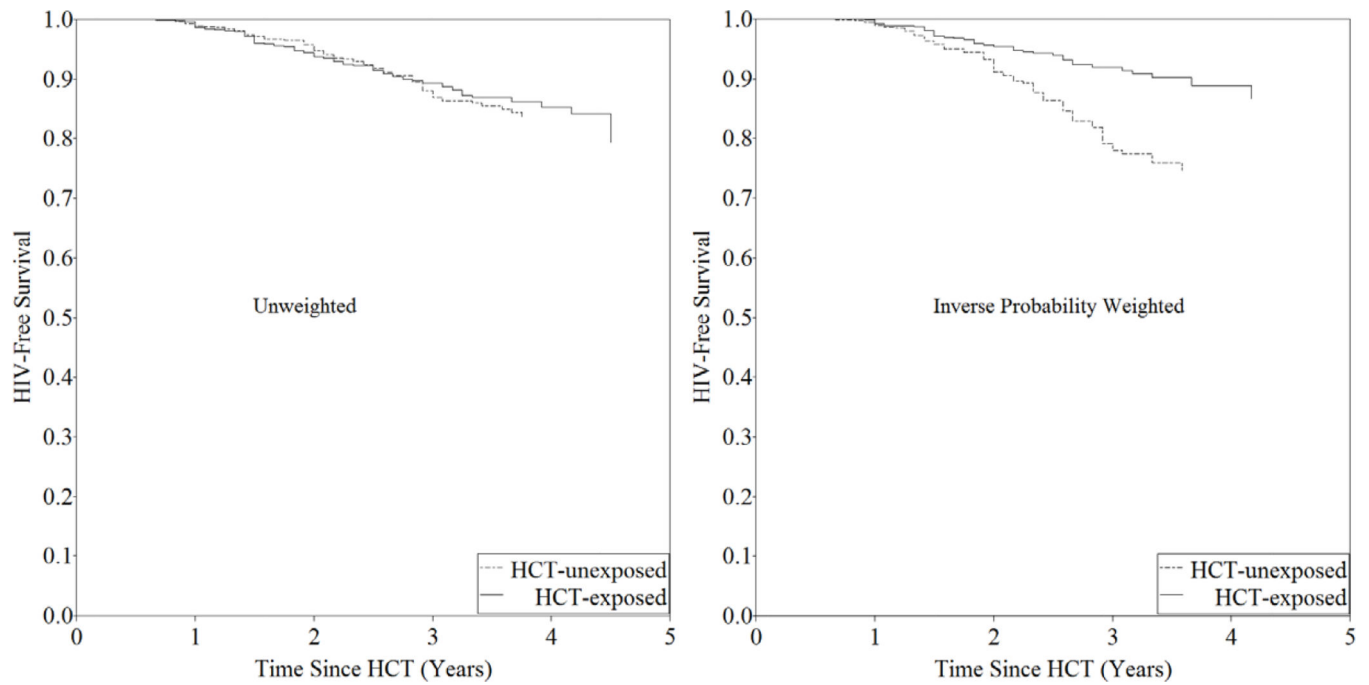


Figure 2. HIV-free Survival by HIV Counseling and Testing Status: Unweighted and Inverse Probability Weighted Curves

Figure 2 depicts the unweighted and weighted Kaplan Meier survival curves comparing those who were HCT-unexposed to those who were HCT-exposed. The inverse probability weighted graph is constructed in a population with time divided into person-months.

Table 1

Characteristics of the Study Population

Table 1 displays the distribution of factors between in the HCT-exposed and HCT-unexposed groups observed at the origin. Covariate totals may not add up to the column total due to missing data.

	HCT-unexposed N=2792	HCT-exposed N=1167	Total N=3959
Gender			
Female	1247 45%	690 59%	1937 49%
Male	1545 55%	477 41%	2022 51%
Age			
15–19	2268 81%	856 73%	3124 79%
20–24	524 19%	311 27%	835 21%
Year of study entry			
2006	1887 68%	609 52%	2496 63%
2007	553 20%	220 19%	773 20%
2008	309 11%	273 23%	582 15%
2009	43 2%	65 6%	108 3%
Distance to Nearest Clinic			
<2 km	838 30%	410 35%	1248 32%
2–5 km	1398 50%	559 48%	1957 49%
>5km	556 20%	198 17%	754 19%
Education			
primary	657 25%	206 19%	863 23%
some secondary	1801 68%	719 66%	2520 67%
secondary	188 7%	170 16%	358 10%
Reported sexual debut			
Yes	728 29%	465 47%	1193 34%
No	1749 71%	532 53%	2281 66%
Condom Use at Last Sex (among sexually active)			
Yes	305 43%	192 42%	497 43%
No	407 57%	261 58%	668 57%
Sex Partners in Last 12 months*			

	HCT-unexposed N=2792	HCT-exposed N=1167	Total N=3959
0	1799 73%	555 56%	2354 68%
1	595 24%	384 39%	979 28%
2	82 3%	46 5%	128 4%
Ever Pregnant (females)			
Yes	159 14%	146 24%	305 17%
No	984 86%	462 76%	1446 83%
Ever Father (males)			
Yes	51 4%	34 8%	85 5%
No	1341 96%	381 92%	1722 95%

Table 2
Incidence of HIV Acquisition by HCT Exposure and Covariates

Table 2 presents number of events, person years, incidence rates, and confidence intervals by time-fixed and time-varying variables.

Variable	Events	PYs	IR	(95% CI)
HCT				
Unexposed	131	4702	2.79	(2.35, 3.31)
Exposed	117	3834	3.05	(2.55, 3.66)
Gender				
Female	190	4344	4.37	(3.79, 5.04)
Male	58	4193	1.38	(1.07, 1.79)
Age				
15–19	188	6570	2.86	(2.48, 3.30)
20–24	60	1966	3.05	(2.37, 3.93)
Distance to Nearest Clinic				
<2 km	81	2804	2.89	(2.32, 3.59)
2–5 km	129	4166	3.10	(2.61, 3.68)
>5km	38	1567	2.43	(1.76, 3.33)
Education				
primary	41	1724	2.38	(1.75, 3.23)
some secondary	177	5733	3.09	(2.66, 3.58)
secondary	30	1080	2.78	(1.94, 3.97)
Reported sexual debut				
Yes	171	3731	4.58	(3.95, 5.32)
No	77	4806	1.60	(1.28, 2.00)
Condom use at last sex				
Yes	56	1397	4.01	(3.08, 5.21)
No	115	2333	4.93	(4.11, 5.92)
Sex Partners in Last 12 months				
0	84	4859	1.73	(1.40, 2.14)
1	152	3291	4.62	(3.94, 5.42)
2	12	389	3.10	(1.76, 5.46)

Variable	Events	PYs	IR	(95% CI)
Ever Pregnant (females)				
Yes	78	1153	6.77	(5.42, 8.45)
No	112	3191	3.51	(2.92, 4.22)
Ever Father (males)				
Yes	6	219	2.72	(1.22, 6.04)
No	52	3972	1.31	(1.00, 1.72)

PY=person-year; IR=incidence rate; CI=confidence interval

Table 3
Hazard Ratios Comparing HCT-Exposed to HCT-Unexposed Participants

All hazard ratios compare the hazard of HIV acquisition among HCT-exposed to HCT-unexposed participants. The main unweighted analysis displays the results of a model with no weights and the main weighted analysis displays the results of a model with inverse probability of exposure and censoring weights. The three stratified analyses display the results of the main weighted model with interaction terms (for gender, age, and time since HCT). Sensitivity analyses display results of main effect models in a non-imputed dataset (i.e. a complete case analysis), in a model with only exposure weights, and in model with standard covariate adjustment, rather than weights. Except in the specified sensitivity analysis, all models are implemented in a dataset with imputed values. All models are implemented in a discrete time dataset.

	HR	(95% CI)
<u>Main Analyses</u>		
Unweighted	1.02	(0.79, 1.31)
Weighted	0.59	(0.45, 0.78)
<u>Stratified Analyses (weighted and imputed)</u>		
Gender Stratified		
Women	0.57	(0.41, 0.78)
Men	0.66	(0.37, 1.18)
Age Stratified		
15–19	0.59	(0.43, 0.82)
20	0.54	(0.31, 0.97)
Time Stratified		
1.5 years	0.65	(0.40, 1.05)
>1.5 years	0.57	(0.40, 0.79)
<u>Sensitivity Analyses</u>		
Weighted, complete case	0.64	(0.46, 0.89)
Weighted with exposure weights only	0.59	(0.44, 0.78)
Covariate Adjusted	0.65	(0.50, 0.86)

HCT=HIV counseling and testing, HR=hazard ratio, CI=confidence interval