Circumcision and risk of HIV among males from Ontario, Canada

Nayan M, Hamilton RJ, Juurlink DN, Austin PC, Jarvi KA

DOI: 10.1097/JU.0000000000002234
Reference: JU-21-1333

To appear in: *The Journal of Urology*
Accepted Date: 02 Sep 2021

Please cite this article as: Nayan M, Hamilton RJ, Juurlink DN, Austin PC, Jarvi KA, Circumcision and risk of HIV among males from Ontario, Canada, *The Journal of Urology®* (2021), doi: 10.1097/JU.0000000000002234.

The Journal of Urology Publish Ahead of Print
DOI: 10.1097/JU.0000000000002234

Circumcision and risk of HIV among males from Ontario, Canada

Madhur Nayan[1], MDCM, PhD, Robert J. Hamilton[1], MD, MPH,
David N. Juurlink[2, 3], MD, PhD, Peter C. Austin[2], PhD, Keith A. Jarvi[4], MD

[1] Division of Urology, Departments of Surgery and Surgical Oncology, Princess Margaret Cancer Centre, University Health Network and the University of Toronto, Toronto, Canada

[2] ICES, Toronto, Canada

[3] Departments of Medicine and Pediatrics, University of Toronto, Toronto, Canada

[4] Division of Urology, Department of Surgery, Mount Sinai Hospital, University of Toronto, Toronto, Canada; Faculty of Medicine, Institute of Medical Science, University of Toronto, Toronto, Canada; Lunenfeld Tannenbaum Research Institute, Mount Sinai Hospital, Toronto, Canada

Correspondence to: Madhur Nayan
Division of Urology, Department of Surgery
Princess Margaret Cancer Centre, University Health Network
610 University Ave 3-130, Toronto, Ontario, Canada, M5G 2M9
t: 857-424-8798 f: 416-946-6590
E-mail: madhur.nayan@mail.utoronto.ca

Runninghead: Circumcision and risk of HIV in Ontario, Canada

Key words: Circumcision; HIV prevention; Intervention

Manuscript word count: 2460

ABSTRACT

Purpose: Randomized trials from Africa demonstrate that circumcision reduces the risk of acquiring HIV among males. However, few studies have examined this association in Western populations. We sought to evaluate the association between circumcision and the risk of acquiring HIV among males from Ontario, Canada.

Materials and Methods: We conducted a population-based matched cohort study of residents in Ontario, Canada. We identified males born in Ontario who underwent circumcision at any age between 1991 and 2017. The comparison group consisted of age-matched males who did not undergo circumcision. The primary outcome was incident HIV. We used cause-specific hazard models to evaluate the hazard of incident HIV. We performed several sensitivity analyses to evaluate the robustness of our results: matching on institution of birth, varying the minimum follow-up period, and simulating various false-negative and false-positive thresholds.

Results: We studied 569,950 males, including 203,588 who underwent circumcision and 366,362 who did not. The vast majority (83%) of circumcisions occurred prior to age 1 year. In the primary analysis, we found no significant difference in the risk of HIV between groups (adjusted hazard ratio 0.98 (95% confidence interval 0.72 to 1.35)). In none of the sensitivity analyses did we find an association between circumcision and risk of HIV.

Conclusions: We found that circumcision was not independently associated with the risk of acquiring HIV among males from Ontario, Canada. Our results are consistent with clinical guidelines that emphasize safe-sex practices and counselling over circumcision as an intervention to reduce the risk of HIV.

INTRODUCTION

Early descriptions of an inverse association between the prevalence of HIV and circumcision led to the hypothesis that circumcision could reduce the risk of acquiring HIV[1]. Since then, three randomized trials conducted in Uganda[2], Kenya[3], and South Africa[4] and several observational studies have evaluated this association. A recent meta-analysis of 49 studies involving a total of 198,125 subjects found that circumcision was associated with a 42% reduced risk of acquiring HIV[5].

Potential explanations for the apparent protection provided by circumcision include decreased risk of intercourse-related microabrasions that may facilitate virus entry[6], reduced surface area of Langerhans cells, one of the initial targets for HIV following sexual exposure[7], and reduced risk of co-infection with an ulcerative or inflammatory sexually transmitted infection that may increase susceptibility to HIV[8].

Despite the available data, there continues to be uncertainty regarding the role of circumcision in reducing the risk of acquiring HIV, particularly in Western populations as the randomized trials conducted in Africa may not be generalizable to populations where HIV prevalence is lower and transmission is more common among men who have sex with men (MSM) or via intravenous drug-use. Although observational studies exist in Western populations, they focus exclusively on MSM[5]. No population-based study has explored the potential role of circumcision as a public health intervention to reduce the risk of HIV. We examined this association among males born in Ontario, Canada.

MATERIALS AND METHODS

Setting

We conducted a population-based matched cohort study of males born in Ontario, Canada. Residents of Ontario have universal access to physician services and hospital care. This study was approved by the Research Ethics Board of Mount Sinai Hospital, Toronto, Ontario.

Data sources

We obtained physician claims data from the Ontario Health Insurance Plan (OHIP) database. We obtained hospitalization data from the Canadian Institute for Health Information[9] (CIHI) Discharge Abstract Database and Same Day Surgery Database, which contain detailed clinical information regarding admissions to hospitals and outpatient surgical procedures, respectively. We obtained basic demographic data from the Registered Persons Database, a registry of all Ontario residents eligible for health insurance. These databases were linked in an anonymous fashion using encrypted health card numbers, and are routinely used to study the long-term consequences of medical care[10, 11]. Details regarding these databases have been described elsewhere[12].

Study Participants

We identified all males born in Ontario who underwent a circumcision at any age between April 1, 1991 and March 31, 2017 using physician claims data and hospitalization codes (Supplemental methods 1) from the OHIP and CIHI databases, respectively. These dates were based on the data available at the time of analysis. These databases and codes have been previously used to study the association between circumcision and infant urinary tract infections in Ontario, Canada[10]. Both databases have been shown to have strong validity for surgical procedures[9, 13].

We required that all study subjects be born in Ontario to avoid potential misclassification of those undergoing circumcision prior to immigration to Ontario. We also required that the subjects have follow-up beyond age 14 years, because our objective was to evaluate the association between circumcision and risk of acquiring HIV through sexual transmission. This age was chosen *a priori* based on a study demonstrating that approximately 10% of Canadian males reported their age of first intercourse being younger than 15 years[14]. We varied the minimum follow-up threshold in a sensitivity analysis described below.

For each male who underwent circumcision and met inclusion criteria, we selected up to 10 males who did not undergo circumcision, matching on date of birth (+/- 30 days).

The index date was defined as the age of presumed sexual activity (14 in the primary analysis) or the date of circumcision (corresponding date based on the date of birth in the control group), whichever occurred later. We excluded those with a diagnosis of HIV prior to the index date.

Outcome Assessment

The primary outcome was incident HIV, defined as the first recorded date of HIV diagnosis in the HIV database. This database was derived in Ontario using similar databases to the present study and has been validated with a sensitivity of 96.2% and specificity of 99.6%[15]. This database has been used in several studies to explore the care and outcomes of patients with HIV in Ontario[16, 17].

We followed subjects until incidence of HIV, date of last contact with health services, death, or March 31st, 2018, whichever occurred first.

Covariates

To address possible confounding related to socioeconomic status[18], we performed an analysis adjusting for estimated income quintile using census-reported median income of the forward sortation area[19], a geographical unit denoted by the first three characters of the Canadian postal code.

Statistical Methods

We compared baseline differences between the circumcised and non-circumcised groups with standardized differences[20], defining imbalance as values greater than 0.20 (small effect size)[21]. We obtained crude estimates of HIV incidence over time using the cumulative incidence function. We estimated median follow-up with the reverse Kaplan-Meier method. We conducted time-to-event analyses using cause-specific hazard models that account for the competing risk of death to estimate the association between circumcision and the rate of incident HIV. We used a robust variance estimator in the Cox models to account for the matched nature of the sample. The proportional hazards assumption was verified by plotting Schoenfeld residuals against time and by including interactions between the underlying time scale and each variable in the model.

All statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC).

Sensitivity Analysis

To test the robustness of our findings, we performed four additional analyses. First, to further reduce potential heterogeneity between the circumcised and non-circumcised groups, we matched additionally on the institution at birth. Second, due to uncertainty regarding the age at which individuals become sexually active, we evaluated ages 12 and 18 as alternative thresholds for minimum follow-up. Third, given the potential for misclassification of circumcision status, we evaluated various thresholds of sensitivity and specificity of the exposure. The thresholds were chosen *a priori* (Supplemental methods 2). Finally, to evaluate unmeasured confounding, we calculated the E-value[22]. Briefly, E-values represent the minimum strength of association that an unmeasured confounder would need to have with both the exposure and outcome to move the observed estimate to any other value (Supplemental methods 3).

RESULTS

Over the 26-year study period, we identified 256,941 males born in Ontario who underwent circumcision and who had follow-up to at least age 14 years. Of these, we matched 203,589 (79%) to 366,363 males who did not undergo circumcision. Non-matched circumcised subjects tended to be from earlier years of the study, likely reflecting the decreasing use of circumcision over time in Ontario[23] and were more likely to be from a rural area (Supplemental table 1), likely reflecting the lower number of births in rural areas. After excluding subjects with a diagnosis of HIV prior to the index date (fewer than 6 subjects, not further described for privacy compliance), the final study cohort consisted of 569,950 males (Table 1). There were no major imbalances between the groups. The majority (83%) of circumcisions occurred prior to the age of 1. Median follow-up was 6.2 (interquartile range (IQR) 3.4 to 9.0) years.

Incident HIV

We identified 142 incident cases of HIV, of which 51 occurred in the circumcised group and 91 in the non-circumcised group. The median age at HIV diagnosis was 21.8 (IQR 20.6 to 23.7) and 22.2 (IQR 20.6 to 23.6) years in the circumcised and non-circumcised group, respectively.

Figure 1 demonstrates the cumulative probability of incident HIV, stratified by circumcision status.

In the unadjusted analysis, circumcision was not significantly associated with the hazard of incident HIV (hazard ratio 0.87, 95% confidence interval 0.60-1.27). In the adjusted analysis, the association between circumcision and HIV was brought closer to the null (hazard ratio 0.98, 95% confidence interval 0.72-1.35, Table 2).

Sensitivity Analysis

The results of the sensitivity analyses are shown in Figure 2, all of which demonstrated no significant association between circumcision and risk of HIV.

Using the pooled effect size (relative risk 0.44[5]) from the randomized trials as the true causal effect, we calculated an E-value of 3.88 for the estimate and 2.37 for the confidence interval. This means that an unmeasured confounder associated with both circumcision and HIV, each by risk ratios of at least 3.88, could move the observed adjusted hazard ratio of 0.98 to 0.44, but confounding weaker than that could not. Furthermore, the risk ratio of the unmeasured confounder's association with both the exposure and outcome would each have to be at least 2.37-fold to explain away the observed upper confidence limit crossing the null, but weaker confounding could not.

DISCUSSION

The role of circumcision in reducing the risk of acquiring HIV remains controversial. Several societies acknowledge the randomized trials from Uganda, Kenya, and South Africa which demonstrate its efficacy, but also caution that these results may not be generalizable to areas where HIV prevalence and transmission patterns differ[24-26]. Our study of 569,950 males from Ontario, Canada, found no significant association between circumcision and the risk of acquiring HIV. These findings support that the effectiveness of circumcision as a public health intervention to reduce the risk of HIV will likely vary depending on the population.

To date, three randomized trials from eastern and southern Africa have evaluated the association between circumcision and HIV[2-4]. Pooled results from these trials demonstrated that circumcision significantly reduced the risk of acquiring HIV by 56%[5]. If efficacy of this magnitude were generalizable to other populations, circumcision would represent one of the most effective surgical interventions in primary infection prevention and wider adoption would be encouraged. However, the efficacy of any intervention varies based on the characteristics of the population; in the context of this study, it is expected that the ability of circumcision to reduce the risk of acquiring HIV would be diminished where HIV prevalence is lower. In Ontario, the estimated prevalence of HIV is less than 0.2%[27], much lower than the reported prevalence of 25% and 18% among the Luo people, who comprised the majority of participants in the Kenyan trial[3]. Furthermore, it has been shown that the protective association between circumcision and risk of HIV is stronger in heterosexual males compared to MSM[5]. Therefore, the magnitude of the effect of circumcision may also be diminished in populations where HIV is transmitted more commonly among MSM, as well as in populations where injection drug use accounts for a larger proportion of cases, as is the case in Ontario[28], Canada[29], and USA[30]. These differences in population characteristics may explain why our results differ from the randomized trials from Africa.

A few observational studies evaluating circumcision and risk of HIV have been done in Western countries. However, many of these have been criticized for the potential misclassification of the exposure and outcome[26]. Furthermore, these studies evaluated only MSM and were of limited sample size.[5]. Our study is the largest to date on this topic and represents the first to evaluate the association of circumcision and HIV among a relatively unselected Western population. Our results are strengthened by using validated databases to identify both the exposure and outcome. While the circumcision procedure code has not specifically been validated, several other surgical procedures have been shown to have high sensitivity and positive predictive value[9, 13]; we anticipate a high positive predictive value for circumcision given the young age and male sex of all subjects. We acknowledge that circumcision performed outside of a medical setting, such as those performed for religious reasons, would not be identified in our method of assessing exposure. Additionally, we recognize that the databases used are administrative in nature and prone to coding errors. However, we evaluated the robustness of our results to varying thresholds of sensitivity and specificity and found consistent results demonstrating a lack of significant benefit from circumcision in reducing the risk of acquiring HIV.

Additional strengths of this study include its generalizability and extended follow-up. While the population-based approach has the advantage of generalizability, it also suffers from heterogeneity. It is therefore possible that the effect of circumcision varies among sub-populations in Ontario. As mentioned, it has been suggested that the strength of association varies according to sexual orientation[5]. We were unable to adjust for this factor as these data are not available. There may be additional characteristics that differ between the circumcised and non-circumcised groups that we did not account for, including sexual (eg, number of partners, condom use, transactional sexual intercourse, etc.) and non-sexual (eg, intravenous drug use) risk behaviours, limiting the ability of our study to measure the direct effect of circumcision on risk of acquiring HIV. However, there is conflicting evidence on the influence of circumcision on sexual risk behaviours[2-4] and it is unlikely that circumcision status is associated with intravenous drug use. Furthermore, the purpose of this study was to evaluate the potential effect of a public health intervention to reduce the risk of HIV, rather than the effect in particular subgroups. It is therefore important to emphasize that our results should therefore be interpreted on the Ontario population-level, and it remains possible that circumcision is an effective method in reducing the risk of HIV in particular subgroups.

Further limitations of this study include the inability to capture HIV diagnosed beyond age 26, given the limitations of the inception dates of the databases. Although most cases of HIV are transmitted sexually and this is beyond the onset of sexual activity for the majority of the studied population[14], it remains conceivable that a protective effect of circumcision might become evident with longer follow-up. Additionally, our cohort included a sample that had not become sexually active during follow-up; this could bias the results towards the null, particularly if this was overrepresented in the non-circumcised group. However, it is anticipated that this sample is small and distributed equally between groups; therefore, their inclusion should not meaningfully impact the results; furthermore, inclusion of these subjects, as was done in the previous trials on this topic[2-4], follows the intention-to-treat principle of a randomized trial.

Despite these limitations, this study is the largest to date and the first to provide information on the association of circumcision and HIV in a relatively unselected Western population. The sensitivity analyses lend support to the robustness of the findings and the estimated E-value suggests that considerable unmeasured confounding would be required to meaningfully influence the results. Given that a randomized trial on this topic is unlikely to ever occur in a Western population, our results can help inform policy and recommendations regarding the use of circumcision in these areas.

CONCLUSION

We found that circumcision was not independently associated with the risk of acquiring HIV among men from Ontario, Canada. These findings differ from the randomized trials from Uganda, Kenya, and South Africa, and support the notion that the magnitude of effect of circumcision in reducing HIV incidence varies based on the population.

ACKNOWLEDGEMENTS

This study was supported in part the Institute for Clinical Evaluative Sciences (ICES), a non-profit research institute sponsored by the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred. Dr. Austin is supported by a Mid-Career Investigator Award from the Heart and Stroke Foundation. The authors thank Joshua Cerasuolo and Refik Saskin from ICES for their assistance in data preparation.

Parts of this material are based on data and information compiled and provided by CIHI. However, the analyses, conclusions, opinions and statements expressed herein are those of the author, and not necessarily those of CIHI.

REFERENCES

1. Fink, A. J.: A possible explanation for heterosexual male infection with AIDS. The New England journal of medicine, **315:** 1167, 1986
2. Gray, R. H., Kigozi, G., Serwadda, D. et al.: Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. The Lancet, **369:** 657, 2007
3. Bailey, R. C., Moses, S., Parker, C. B. et al.: Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. The lancet, **369:** 643, 2007
4. Auvert, B., Taljaard, D., Lagarde, E. et al.: Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS medicine, **2**, 2005
5. Sharma, S. C., Raison, N., Khan, S. et al.: Male circumcision for the prevention of human immunodeficiency virus (HIV) acquisition: a meta-analysis. BJU international, **121:** 515, 2018
6. Mehta, S. D., Krieger, J. N., Agot, K. et al.: Circumcision and reduced risk of self-reported penile coital injuries: results from a randomized controlled trial in Kisumu, Kenya. The Journal of urology, **184:** 203, 2010
7. Hussain, L., Lehner, T.: Comparative investigation of Langerhans' cells and potential receptors for HIV in oral, genitourinary and rectal epithelia. Immunology, **85:** 475, 1995
8. Fleming, D. T., Wasserheit, J. N.: From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sexually transmitted infections, **75:** 3, 1999
9. Juurlink, D. N.: Canadian institute for health information discharge abstract database: a validation study: Institute for Clinical Evaluative Sciences, 2006
10. To, T., Agha, M., Dick, P. T. et al.: Cohort study on circumcision of newborn boys and subsequent risk of urinary-tract infection. The Lancet, **352:** 1813, 1998
11. Nayan, M., Hamilton, R. J., Macdonald, E. M. et al.: Vasectomy and risk of prostate cancer: population based matched cohort study. bmj, **355:** i5546, 2016
12. Nayan, M., Macdonald, E. M., Juurlink, D. N. et al.: Medication use and survival in diabetic patients with kidney cancer: A population-based cohort study. Pharmacol Res, **113:** 468, 2016
13. Salata, K., Hussain, M. A., de Mestral, C. et al.: Validation of abdominal aortic aneurysm repair codes in Ontario administrative data. Clinical and Investigative Medicine, **41:** E148, 2018
14. Canada, S.: National Household Survey, Statistics Canada Catalogue no. 82-003-X. 2015
15. Antoniou, T., Zagorski, B., Loutfy, M. R. et al.: Validation of case-finding algorithms derived from administrative data for identifying adults living with human immunodeficiency virus infection. PloS one, **6**, 2011
16. Kendall, C. E., Taljaard, M., Younger, J. et al.: A population-based study comparing patterns of care delivery on the quality of care for persons living with HIV in Ontario. BMJ open, **5**, 2015
17. Kendall, C. E., Wong, J., Taljaard, M. et al.: A cross-sectional, population-based study measuring comorbidity among people living with HIV in Ontario. BMC public health, **14:** 1, 2014
18. Morris, B. J., Bailis, S. A., Wiswell, T. E.: Circumcision rates in the United States: rising or falling? What effect might the new affirmative pediatric policy statement have? Mayo Clin Proc, **89:** 677, 2014
19. Minaker, L. M., McCargar, L., Lambraki, I. et al.: School region socio-economic status and geographic locale is associated with food behaviour of Ontario and Alberta adolescents. Canadian Journal of Public Health, **97:** 357, 2006
20. Yang, D., Dalton, J. E.: A unified approach to measuring the effect size between two groups using SAS®. Presented at the SAS global forum, 2012
21. Sawilowsky, S. S.: New effect size rules of thumb. Journal of Modern Applied Statistical Methods, **8:** 26, 2009

22. VanderWeele, T. J., Ding, P.: Sensitivity analysis in observational research: introducing the E-value. Annals of internal medicine, **167:** 268, 2017
23. Goel, V., Williams, J. I., Anderson, G. M. et al.: Patterns of health care in Ontario. The ICES practice atlas, **2**, 1996
24. Sorokan, S. T., Finlay, J. C., Jefferies, A. L.: Newborn male circumcision. Paediatr Child Health, **20:** 311, 2015
25. Dave, S., Afshar, K., Braga, L. H. et al.: Canadian Urological Association guideline on the care of the normal foreskin and neonatal circumcision in Canadian infants (full version). Canadian Urological Association Journal, **12:** E76, 2018
26. American Association of Urology. (2018). *Circumcision.* Retreived from auanet.org/guidelines/guidelines/circumcision
27. Antoniou, T., Zagorski, B., Bayoumi, A. M. et al.: Trends in HIV prevalence, new HIV diagnoses, and mortality among adults with HIV who entered care in Ontario, 1996/1997 to 2009/2010: a population-based study. Open medicine : a peer-reviewed, independent, open-access journal, **7:** e98, 2013
28. Wheeler, K. M., Antoniou, T., Gardner, S. et al.: Sociodemographic and Health Profile of Heterosexual Men Living With HIV in Ontario, Canada. American journal of men's health, **11:** 855, 2017
29. Challacombe, L.: The epidemiology of HIV in Canada. Canadian AIDS treatment information exchange. Retrieved from http://www. catie. ca/fact-sheets/epidemiology/epidemiologyhiv-canada, 2015
30. Linley, L., Johnson, A. S., Song, R. et al.: Estimated HIV incidence and prevalence in the United States, 2014–2018. 2020

FIGURE LEGENDS

Figure 1: Cumulative incidence of HIV by circumcision status.

Figure 2: Sensitivity analyses evaluating the association between circumcision and risk of HIV.

Table 1: Characteristics of circumcised subjects matched to non-circumcised subjects from Ontario, Canada.

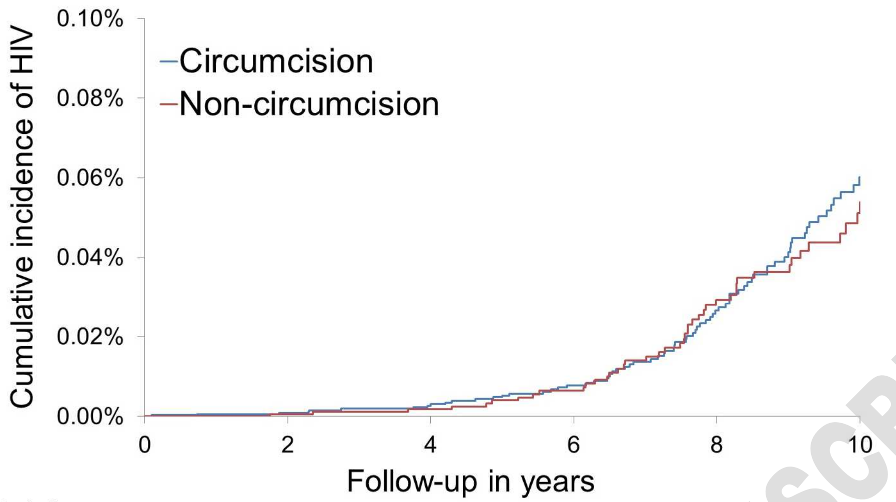
Patient characteristic	**Circumcised (n=203,588)**	**Non-circumcised (n=366,362)**	**Absolute standardized difference**
Age at circumcision (years, median (IQR))	0.088 (0.085 – 0.096)		
Year of cohort entry (n (%))			0.18
1991 – 1995	90607 (44)	137492 (38)	
1996 – 2000	71672 (35)	134851 (37)	
2001 – 2005	30036 (15)	64834 (18)	
2006 – 2010	6560 (3.2)	17418 (4.7)	
2011 – 2016	4713 (2.3)	11767 (3.2)	
Income quintile (n (%))			0.03
Missing	1540 (0.078)	3211 (0.088)	
1 (lowest)	43826 (22)	82259 (22)	
2	40856 (20)	74436 (20)	
3	41501 (20)	72962 (20)	
4	41269 (20)	72091 (20)	
5 (highest)	34596 (17)	34596 (17)	
Rural (n (%))			0.02
Missing	322 (0.0016)	541 (0.0015)	
Yes	29950 (15)	48211 (13)	
No	173316 (85)	317610 (87)	

Abbreviations: IQR: interquartile range

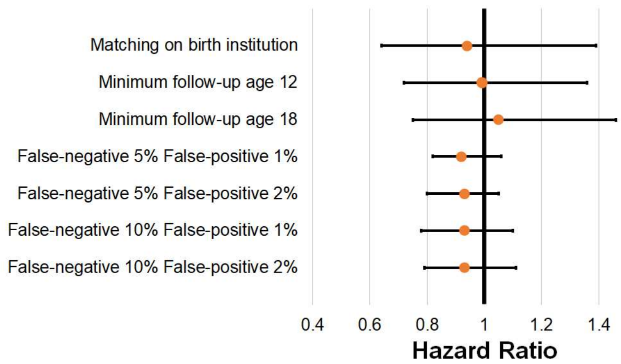
Table 2: Association between circumcision and rate of incident HIV among 569,950 males in Ontario, Canada.

	Unadjusted (HR (95% CI))	**Adjusted (HR (95% CI))**
Circumcised (yes vs. no)	0.87 (0.60 – 1.27)	0.98 (0.72 – 1.35)
Income quintile		
1 (lowest)	Reference	Reference
2	0.50 (0.28 – 0.92)	0.51 (0.31 – 0.82)
3	0.65 (0.31 – 1.34)	0.65 (0.36 – 1.16)
4	0.30 (0.14 – 0.67)	0.30 (0.16 – 0.58)
5 (highest)	0.34 (0.15 – 0.80)	0.35 (0.18 – 0.66)

Abbreviations: CI: confidence interval; HR: hazard ratio



Number at risk						
Circumcision	366362	310834	250914	185021	118619	54051
Non-circumcision	203588	177140	147957	113729	76919	36544


Matching on birth institution
Minimum follow-up age 12
Minimum follow-up age 18
False-negative 5% False-positive 1%
False-negative 5% False-positive 2%
False-negative 10% False-positive 1%
False-negative 10% False-positive 2%
0.4
0.6
0.8
1
1.2
1.4
Hazard Ratio