Poster # 966

# Antiretroviral therapy reduces HIV shedding from male circumcision wounds: a prospective study of HIV-infected men in Rakai, Uganda


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## Abstract:

**Background:** A randomized trial of circumcision of HIV-positive men reported increased HIV transmission to female partners among men who resumed sexual intercourse prior to wound healing. We conducted a prospective study in Rakai, Uganda to assess HIV shedding post-male circumcision (MC).

**Methods:** HIV shedding was evaluated among 236 HIV-infected men (183 self-reported ART-naïve, 11 self-reported ART with detectable plasma viral load (VL), and 29 self-reported ART with undetectable plasma VL). Preoperative and weekly penile lavages for 6 weeks were tested for HIV shedding and VL using a real-time quantitative PCR assay (Abbott Molecular, Abbott Park, IL). Adjusted prevalence risk ratios (AdjPRRs) of HIV shedding were estimated using Poisson multivariate regression models with generalized estimating equations and robust variance.

**Results:** HIV shedding was detected among 39.3% (72/183) of the ART-naive men and was significantly increased after MC at weeks one (PRR=1.87,95%CI=1.12-3.14), two (PRR=3.17, 95%CI=1.95-5.14), and three (PRR=2.00, 95%CI=1.21-3.31), then decreased by week six after wound healing (PRR=0.28, 95%CI=0.09-0.84). HIV shedding was most common among men with an HIV plasma VL>50,000 copies/mL compared to men with VL<400 copies/mL (PRR=13.06, 95%CI=5.19-32.90). HIV shedding was significantly lower among men on ART with undetectable plasma VL (adjPRR=0.12, 95%CI=0.04-0.39). Among men with detectable HIV shedding, the median HIV $log_{10}$VL was significantly lower with VL suppressed by ART (1.93, IQR=1.83-2.14) compared to ART-naïve men (2.67, IQR=2.30-3.22,p<0.001).

**Interpretation:** ART significantly decreases the frequency and quantity of shedding from male circumcision wounds. In addition to sexual abstinence and condom use, ART prior to MC may be considered to reduce male-to-female HIV transmission.


## Background:

- Three randomized controlled trials demonstrated that male circumcision (MC) significantly decreases heterosexual HIV acquisition in men by 50% to 60%.
- However, MC of HIV-positive men increased HIV transmission to their female partners among men who engaged in sexual intercourse prior to wound healing.
- Even with counseling of sexual abstinence, greater than 65% of married men and approximately 30% of all men report resuming sexual intercourse prior to wound healing.
- Thus, a better understanding of the pathophysiology by which MC might increase transmission of HIV to female partners and possible prevention methods in the immediate post-surgical period is urgently needed.

## Methods:

- A prospective cohort study between June 2009 and April 2012 was conducted in Rakai, Uganda to assess HIV shedding from MC wounds.
- All participants were followed weekly for six weeks and then at eight and twelve weeks.
- Men had a lavage at the coronal sulcus, which involved non-traumatic washing with 5 mL of phosphate buffered saline (PBS) (pH 7.2) at enrollment and each follow-up visit.
- MC lavage samples were assessed using a modified Abbott Real-Time HIV-1 Assay (Abbott Laboratories. Abbott Park, Illinois) with a detection limit of 40 copies/mL.
- Adjusted prevalence risk ratios (AdjPRRs) of HIV shedding were estimated using Poisson multivariate regression models with generalized estimating equations and robust variance.

Figure 1. Study flow diagram

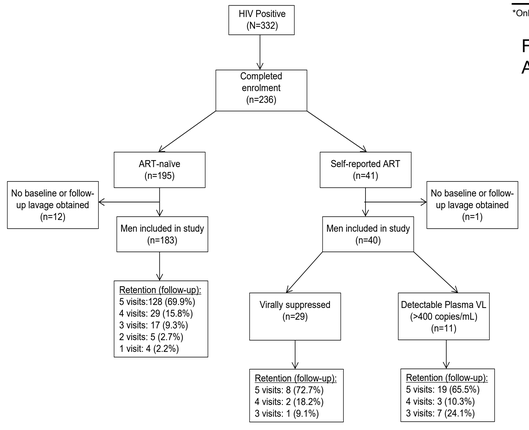
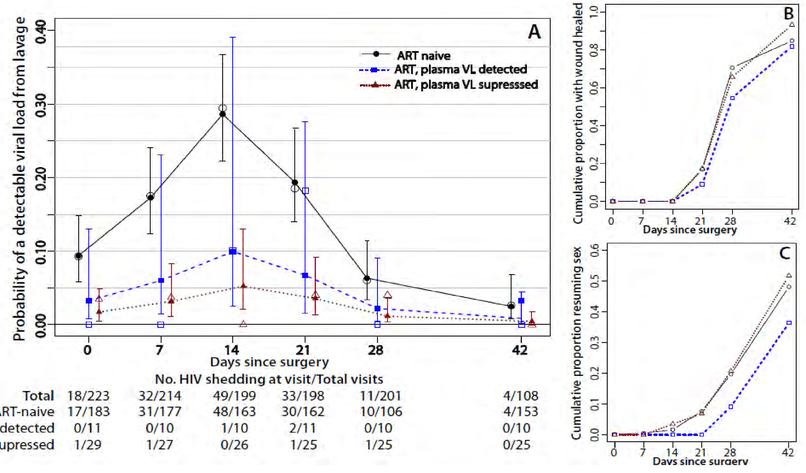



Table 1. Baseline demographics and sexual risk behaviors at enrollment.

| | Self-report | Self-report ART | | p-value |
|---|---|---|---|---|
| | ART-naïve (n=183) | Detectable VL (n=11) | Supressed VL (n=29) | |
| Enrollment age (years) | | | | 0.39 |
| <30 | 71 (38.8%) | 3 (27.3%) | 6 (20.7%) | |
| 30-39 | 79 (43.2%) | 6 (54.5%) | 17 (58.6%) | |
| >40 | 33 (18.0%) | 2 (18.2%) | 6 (20.7%) | |
| Marital Status | | | | 0.53 |
| Not married | 119 (65.0%) | 6 (54.5%) | 20 (69.0%) | |
| Monogamous | 49 (26.8%) | 5 (45.5%) | 8 (27.6%) | |
| Polygamous | 15 (8.2%) | 0 (0.0%) | 1 (3.4%) | |
| Religion | | | | 0.04 |
| Catholic | 135 (73.8%) | 5 (45.5%) | 19 (65.5%) | |
| Protestant | 39 (21.3%) | 3 (27.3%) | 9 (31.0%) | |
| Muslim | 1 (0.5%) | 0 (0.0%) | 0 (0.0%) | |
| Pentecostal or other | 8 (4.4%) | 3 (27.3%) | 1 (3.4%) | |
| Number of sexual partners during past year | | | | 0.005 |
| None | 8 (4.4%) | 1 (9.1%) | 5 (17.2%) | |
| 1 | 58 (31.7%) | 7 (63.6%) | 13 (44.8%) | |
| 2 | 57 (31.1%) | 3 (27.3%) | 8 (27.6%) | |
| 3+ | 60 (32.8%) | 0 (0.0%) | 3 (10.3%) | |
| Condom use past year* | | | | 0.02 |
| None | 102 (60.0%) | 5 (50%) | 9 (37.5%) | |
| Inconsistent use | 53 (31.2%) | 3 (30.0%) | 7 (29.2%) | |
| Consistent use | 15 (8.8%) | 2 (20.0%) | 8 (33.3%) | |
| Genital ulcer disease last 30 days | | | | 0.50 |
| No | 157 (85.8%) | 9 (81.8%) | 27 (93.1%) | |
| Yes | 26 (14.2%) | 2 (18.2%) | 2 (6.9%) | |
| Treatment with septrin | | | | <0.001 |
| No | 142 (77.6%) | 2 (18.2%) | 5 (17.2%) | |
| Yes | 41 (22.4%) | 9 (81.8%) | 24 (82.8%) | |
| CD4 count (cells/uL) | | | | <0.001 |
| <200 | 17 (9.3%) | 6 (54.5%) | 5 (17.2%) | |
| 200-500 | 85 (46.4%) | 4 (36.4%) | 15 (51.7%) | |
| >500 | 81 (44.3%) | 1 (9.1%) | 9 (31.0%) | |
| Median CD4 cell count cells/uL, IQR | 466 (314-655) | 181 (81-249) | 358 (258-534) | <0.001 |
| Median viral load log copies/mL, IQR | 4.6 (4.15-5.16) | 4.98 (4.24-5.31) | | 0.27 |
| Suppressed viral load <400 copies/mL | 17 (9.3%) | 0 (0.0%) | 29 (100.0%) | |

*Only among sexually active men. Data were also missing for five individuals in the ART-naïve group.

Figure 2. HIV shedding from male circumcision wounds, wound healing and resumption of sex stratified by ART and plasma VL status. The open circles and squares are empirical data and closed are the fit estimates.




No. HIV shedding at visit/Total visits

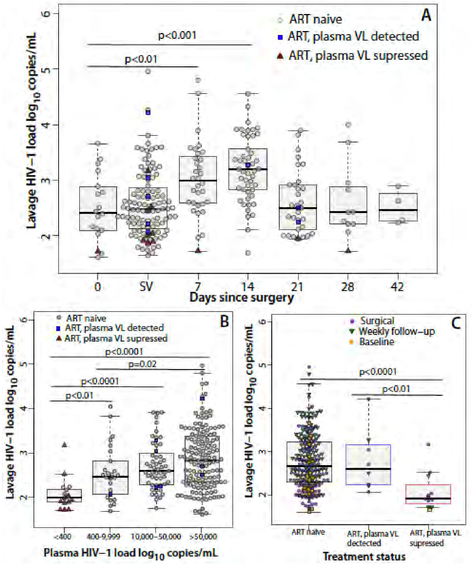
| | | | | | | |
|---|---|---|---|---|---|---|
| Total | 18/223 | 32/214 | 49/199 | 33/198 | 11/201 | 4/108 |
| ART-naive | 17/183 | 31/177 | 48/163 | 30/162 | 10/106 | 4/153 |
| ART, plasma VL detected | 0/11 | 0/10 | 1/10 | 2/11 | 0/10 | 0/10 |
| ART, plasma VL supressed | 1/29 | 1/27 | 0/26 | 1/25 | 1/25 | 0/25 |

Table 2. Associations with the detection of HIV shedding from male circumcision wounds.

| | HIV shedding / visits | Percent (%) | PRR (95% CI) | adjPRR (95% CI)* |
|---|---|---|---|---|
| Age (years) | | | | |
| <30 | 45/348 | 12.9% | 1.00 (referant) | ----- |
| 30-39 | 60/466 | 12.9% | 0.97 (0.59-1.57) | ----- |
| >40 | 24/186 | 12.9% | 0.98 (0.54-1.77) | ----- |
| GUD | | | | |
| No | 112/871 | 12.9% | 1.00 (referant) | ----- |
| Yes | 17/129 | 13.2% | 1.07 (0.61-1.88) | ----- |
| Certified healed wound | | | | |
| No | 118/609 | 19.4% | 1.00 (referant) | 1.00 (referant) |
| Yes | 10/373 | 2.7% | 0.13 (0.07-0.26) | 0.27 (0.10-71) |
| Resumed sex week prior | | | | |
| No | 124/819 | 15.1% | 1.00 (referant) | ----- |
| Yes | 4/163 | 2.5% | 0.12 (0.04-0.46) | ----- |
| HIV shedding prior to MC | | | | |
| No | 105/912 | 11.5% | 1.00 (referant) | 1.00 (referant) |
| Yes | 24/88 | 27.3% | 2.41 (1.44-4.03) | 1.97 (1.21-3.21) |
| CD4 count (cells/uL) | | | | |
| >500 | 44/405 | 10.9% | 1.00 (referant) | 1.00 (referant) |
| 200-500 | 63/465 | 13.5% | 1.23 (0.76-2.00 | 1.27 (0.79-2.05) |
| <200 | 22/130 | 16.9% | 1.49 (0.85-2.63) | 1.84 (1.06-3.18) |
| Plasma viral load | | | | |
| <400 | 4/217 | 1.8% | 1.00 (referant) | ----- |
| 400-9,999 | 13/185 | 7.0% | 4.32 (1.63-11.46) | ----- |
| 10,000-49,000 | 26/224 | 11.6% | 6.33 (2.40-16.71) | ----- |
| >50,000 | 82/336 | 24.4% | 13.06 (5.19-32.90) | ----- |
| Self-report ART and VL | | | | |
| ART naïve | 123/821 | 15.0% | 1.00 (referant) | 1.00 (referant) |
| ART but detectable VL | 3/51 | 5.9% | 0.38 (0.10-1.45) | 0.37 (0.08-1.58) |
| ART and suppressed VL | 3/128 | 2.3% | 0.15 (0.05-0.44) | 0.12 (0.04-0.39) |

*Adjusted analysis includes adjustment for the amount of HIV shedding by weekly visit.

Figure 3. HIV viral load from male circumcision wounds stratified by ART and plasma VL status. SV represents the surgical visit.




## Summary and Conclusions:

- HIV shedding from MC wounds was detected among 39% of ART-naïve HIV-infected men during the wound healing phase, but was significantly decreased among individuals virally suppressed from ART.
- HIV shedding was also most common among men with highest plasma VLs (>50,000 copies/mL), lowest CD4 counts, and those without complete wound healing.
- This is the first study to demonstrate that ART decreases both the number of HIV shedding events and the quantity of virus shed from MC wounds, suggesting that ART may potentially decrease HIV transmission to female partners immediately after MC.
- In addition to sexual abstinence and condom use, ART prior to MC may be considered to reduce male-to-female HIV transmission.