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HIV-1 Plasma RNA and Risk of HIV-1 Transmission

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for the Partners in Prevention HSV/HIV Transmission Study Team

HIV-1 Transmission and HIV-1 RNA

- Risk of HIV-1 heterosexual transmission is strongly associated with HIV-1 plasma RNA level
  - Rakai, Ugandan HIV-1 serodiscordant couples (n=415): *[Quinn et al 2000]*
    - 2.4-fold [95%CI 1.9-3.3] increased risk of HIV-1 transmission per $\log_{10}$ increase in HIV-1 plasma RNA
    - No difference in rates of HIV-1 transmission by gender within strata of HIV-1 RNA
  - Lusaka, Zambian serodiscordant couples (n=1022): *[Fideli et al 2001]*
    - 2.5-fold [95%CI 1.5-4.0] increased risk of Male-to-Female transmission transmission per $\log_{10}$ viral RNA
    - 1.8-fold [95%CI 1.2-2.1] increased risk of Female-to-Male transmission transmission per $\log_{10}$ viral RNA

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Study goals

- Can an intervention that reduces HIV-1 plasma RNA impact heterosexual transmission of HIV-1?
- What level of reduction in HIV-1 plasma RNA is needed to reduce risk of heterosexual transmission of HIV-1 by 50%?

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Study design

- Model HIV-1 plasma RNA and HIV-1 transmission risk data
- Data from Partners in Prevention HSV/HIV Transmission Study - randomized trial of genital herpes (HSV-2) suppression to reduce HIV-1 transmission
  - Epidemiologic studies showing HSV-2 infection increases HIV-1 transmission
  - 5 clinical trials showing HSV-2 suppression w/ acyclovir or valacyclovir given to HIV-1 infected person reduces HIV-1 plasma & genital RNA

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Partners in Prevention HSV/HIV Transmission Study

- HIV-1 serodiscordant couples in East and southern Africa
  - Kenya, Rwanda, Tanzania, Uganda, Botswana, S. Africa, Zambia
  - HIV-1 infected partners also HSV-2+ and CD4 ≥ 250 cells/mm^3
- Both partners followed for ≤24 months
  - Monthly drug (acyclovir 400 mg bid/placebo) to HIV-1+ partner
  - Quarterly specimen collection from both partners
- Primary Study endpoints
  - Quarterly HIV-1 serostatus in HIV-1 susceptible partners
  - Quarterly HIV-1 plasma RNA for HIV-1+ partners
- Transmission linkage confirmed by viral sequencing
  - HIV-1 *env*&*gag* regions sequenced from both partners plasma

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Characteristics of cohort

- Demographics:
  - 3408 HIV-1 serodiscordant couples enrolled
  - 67% of HIV+ partners were female; 65% ≤ 35 yrs old
  - Median partnership duration - 5 yrs
- Behavioral characteristics by report:
  - Reported unprotected sex (no condom use)
    - 29% at baseline; 7% follow-up
  - HIV- partners reported outside partners
    - 5.4% at baseline; 15.5% at 24 mo (no difference by study arm)
- Clinical Characteristics:
  - Median CD4 460 cells/mm^3
  - Median HIV-1 plasma RNA 4.2 $\log_{10}$ copies/ml
  - 331 (9.8%) of HIV+ partners initiated ARV during follow-up

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HIV-1 transmission events

- 151 HIV-1 transmissions events confirmed:
  - 108 (72%) transmissions linked by virus sequencing
  - 40 (26%) transmissions unlinked
  - 3 (2%) unable to link

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Partners in Prevention study results

- Acyclovir did not reduce HIV-1 transmission (HR=0.92 [95%CI 0.6-1.41]) despite significant reduction of
  - 73% in HSV-2+ genital ulcer disease (GUD)
  - 0.25 $\log_{10}$ plasma and ~0.3 $\log_{10}$ genital HIV-1 levels

(Celum et al., IAS, Cape Town 2009)

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Modeling methods

- Examine the relationship of HIV-1 plasma RNA to risk of (linked) seroconversion

- Cox proportionate hazards model
  - Time-varying HIV-1 plasma RNA
  - HIV-1 plasma RNA level and risk of HIV-1 seroconversion modeled to fit a continuous function

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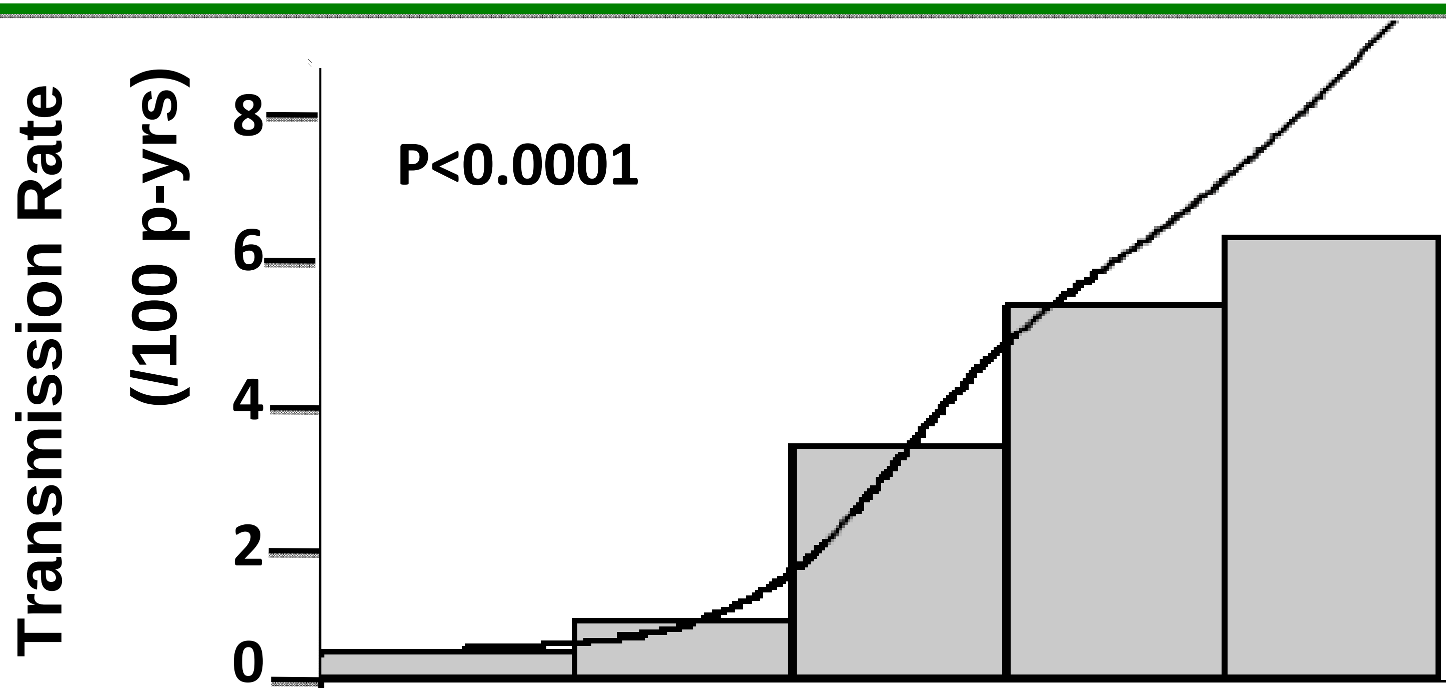
HIV-1 RNA and risk of HIV-1 transmission



# Events	**3**	**10**	**58**	**38**	**3**
P-yrs	954	1382	1772	805	53
Incidence	0.3%	0.7%	2.9%	4.7%	5.7%
95% CI	(0.0 0.9)	(0.3 1.3)	(2.2 3.8)	(3.3 6.5)	(1.2 16.5)

2 3 4 5 6 7

Plasma HIV-1 RNA (Log_{10} copies/ml)

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Impact of HIV-1 plasma RNA reductions on HIV-1 transmission

- Overall transmission rate 2.14/100 p-yrs
  - Compare to Uganda (11.8%) and Zambia (8.6%)

- Based on modeling we predict that
  - 0.75 $\log_{10}$ copies/ml reduction in plasma HIV-1 RNA would be needed for 50% reduction in HIV-1 transmission

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Additional cofactors

- Assess effect of adding previously identified HIV-1 transmission cofactors to this model?
- **RR –** Relative risk of HIV-1 transmission when factor is present compared to when factor is absent
- **p-main effect –**significance of change in HIV-1 transmission with vs. without cofactor after adjusting for HIV-1 RNA level
- **Interaction** with HIV-1 plasma RNA tested for each cofactors and found not significant for any

Additional cofactors assessed

Co-factor	RR	p-maineffect
HIV-1 + male	1.39	0.09
HIV-1 susceptible HSV-2+	1.63	0.04
MaleHIV-1 susceptiblecircumcised	0.53	0.02
HIV-1 susceptible unprotected sex	2.12	0.001
HSV-2 suppression (acyclovir/placebo)	1.04	0.84
MaleHIV-1+ circumcised	0.65	0.19
*ARV initiated in HIV-1+	0.31	0.26
*GUD in HIV-1 susceptible (prior 3 mo)	1.19	0.80
*GUD in HIV-1 + (prior 3 mo)	0.93	0.85

* and n=1, respectively), so values have high uncertainty

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Key conclusions

- Overall HIV-1 transmission rate was lower in this study compared to Ugandan or Zambian cohorts
  - likely due to intensive counseling with high condom use
- Relationship of HIV-1 plasma RNA and HIV-1 transmission was non-linear
- Reduction in HIV-1 transmission by 50% required 0.75 $\log_{10}$ copies/ml reduction in HIV-1 plasma RNA
- Co-factors affect HIV-1 transmission in this model without interaction with HIV-1 plasma RNA

Key limitation

- Relationship ofHIV plasma RNAand HIV-1 transmission evaluated in highly selected population of HIV serodiscordant couples
  - Intensive counseling over 24 months
  - Unprotected sex decreased and sex with outside partners increased during follow-up

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Implications

- Future HIV-1 prevention interventions seeking to lower HIV-1 heterosexual transmission by reducing plasma HIV levels could use the 0.75 $\log_{10}$ copies/ml reduction as a minimum target.
- This could be affected by prevalence of HSV-2 and male circumcision in the susceptible partner and frequency of unprotected sex in the target population
- New studies of non-ARV interventions that can effect such large reductions in HIV-1 plasma RNA are needed.

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