



# Estimating Transmission Probabilities Over Time in Acute HIV Infection From Biological Data

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## ABSTRACT

**Background:** Per coital act transmission probabilities have been defined in chronic but not acute HIV infection. Work in nonhuman primates (Pullium JK et al. *JID* 2001) suggests a parallel correlation between semen and blood viral loads over time during acute HIV infection. We have previously described a probabilistic model estimating male-female transmission as a function of total semen R5 HIV count and endocervical CD4+CCR5+ receptor availability (Chakraborty H et al. *AIDS* 2001). We assessed the impact of predicted changes in semen HIV concentration during acute HIV infection on per coital act transmission probability.

**Methods:** Blood HIV dynamics were described using longitudinal RNA levels from symptomatic acutely infected individuals not on antiretroviral therapy. An average fitted curve was generated using piecewise regression. The blood model assumed a median incubation period of 14 days, initial inoculum of 10<sup>6</sup> copies/mL, and static set point concentration. Predicted semen HIV dynamics were calculated based on this curve and observed semen RNA concentrations at set point. A fixed-concentration ratio between semen and blood from initial infection to set point was assumed. From predicted semen concentrations, per-act male-female transmission probabilities were calculated using our published model given 100% R5 populations in semen, median endocervical CD4+CCR5+ receptor count, and median ejaculate volume.

**Results:** 175 data points from 55 subjects contributed to the blood viral dynamic model. Peak viremia was at 23 days from infection (9 days post symptom onset). Semen HIV dynamics and transmission probabilities were estimated for hypothetical individuals with observed minimum, median, and maximum set point semen RNA concentrations (2.17, 3.85, and 7.12 log copies/mL). Respective per-act probabilities of 0.0015, 0.0308, and 1.000 at peak viremia corresponded to set point probabilities of 0.0001, 0.0018, and 0.8484. Probabilities at peak viremia were 19.7-, 22.2-, and 1.4-fold increased over set point in these examples.

**Conclusions:** Susceptible partners of individuals with acute HIV infection may be at up to 20-fold greater risk per exposure compared to partners of individuals at virologic set point due to higher HIV shedding in semen.

## INTRODUCTION

Acute HIV infection may be an attractive target for public health intervention because it is thought to be associated with high transmission potential.<sup>1,2</sup> The degree to which viral burden in genital fluids contributes to this has been unclear.

It has been asserted that semen viral burden—and hence, infectivity—must be greater during acute infection. Such viral dynamics have been clearly described in the blood compartment.<sup>3-6</sup> Limited evidence from nonhuman primate studies suggests that semen viral loads in acute infection also peak rapidly, changing in tandem with changes in blood.<sup>7</sup>

In this study, we tested the hypothesis that blood and semen dynamics are parallel by a method commonly used in population pharmacokinetics: first developing a semen viral dynamic model assuming this parallel correlation, then testing the validity of this model's predictions against the observed distribution of timed semen concentrations. From the final model, we estimate transmission probabilities using a previously published probabilistic model<sup>8</sup> and some basic assumptions.

## METHODS

**Patients:** Fifty-five patients with well-characterized, acute HIV from previously published studies<sup>6,8,9</sup> contributed 175 longitudinal blood-only data points; 32 had concurrent blood and semen concentrations. Two semen subjects were excluded because of proven STDs. Forty-two HIV+ patients with chronic infection and CD4 >200 were used for comparison.

**HIV RNA:** NASBA/NucliSens (LL, <400 copies/mL) for semen; various for blood plasma. Undetectable results were assigned 0.5 x LL for that assay and compartment.

**Describing Viral Dynamics in Semen:** Observed concentrations were plotted vs time from infection assuming a 14-day incubation period. Regression models were compared using the likelihood ratio test.

**Describing Viral Dynamics in Blood:** A precise average fitted curve for blood data used piecewise regression and polynomial smoothing splines, assuming a day 0 inoculum of 10<sup>6</sup> copies/mL HIV RNA; a 14-day incubation; and blood set point at 120 days.

**Developing a Composite (Final) Semen Model:** A predictive semen curve was made by adjusting the

blood model so that the predicted set point matched the observed median semen concentration for HIV+ patients with CD4 >200.

**Assessing Precision and Bias of the Final Model:** Agreement of model predictions and observed data was assessed by measuring the number of observed data points falling within “prediction bands” around the predicted population mean.

**Estimation of Transmission Probabilities:** Estimated changes in per-act male-female transmission probabilities were calculated from predicted semen HIV burden using a previously published probabilistic model.<sup>8</sup> Median ejaculate volume and cervico-vaginal receptor cell density were assumed.

## RESULTS

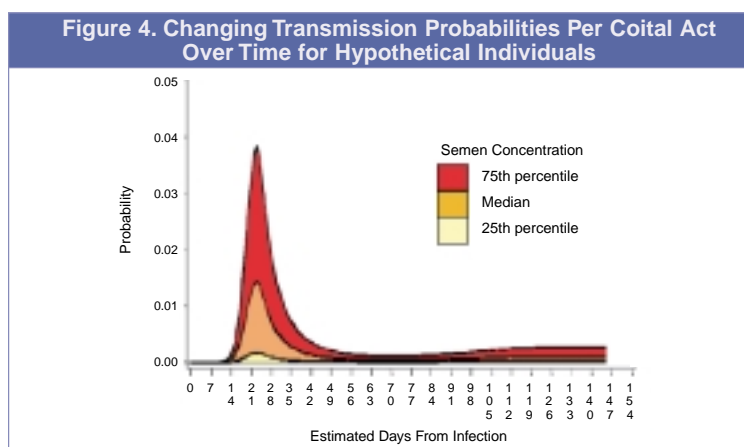
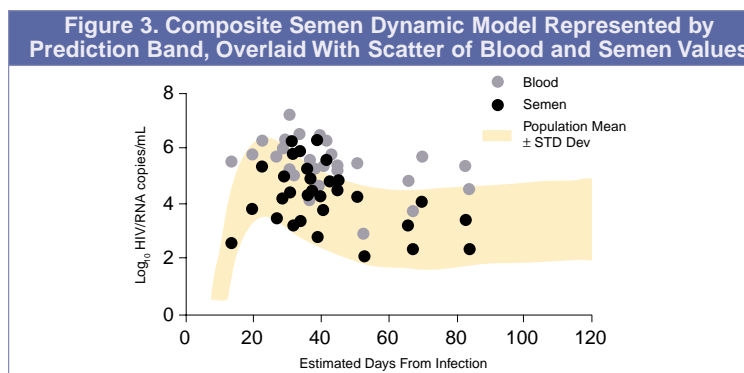
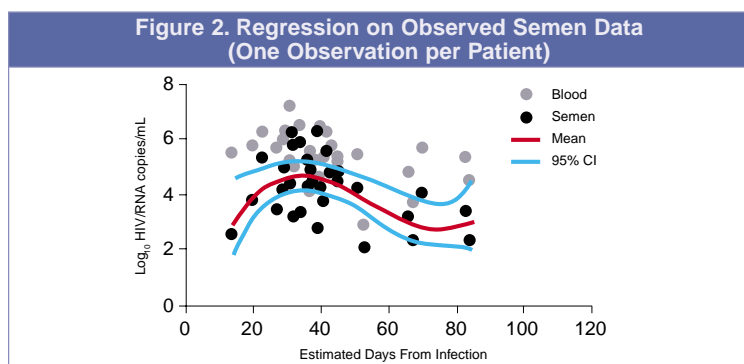
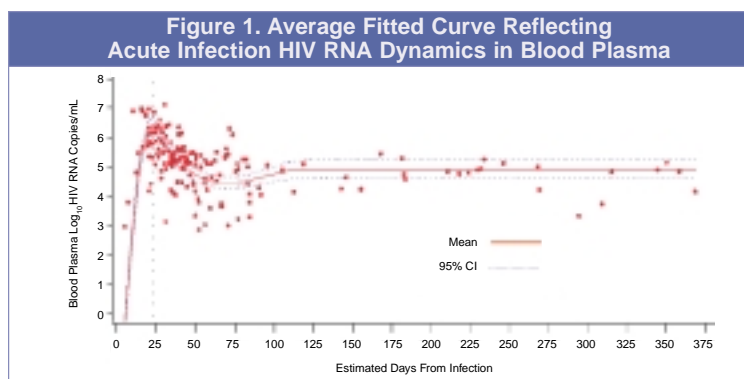
**Blood Model** (Figure 1). The average fitted curve derived from longitudinal blood data was similar to published models; estimated peak viral burden occurred 23 days post infection (9 days post symptoms onset) and was 1.58 log copies/mL greater than set point.

**Semen Data** (Figure 2). Semen HIV burden close to symptoms onset was significantly higher than later in acute infection ( $P = 0.0046$ ) and a cubic regression curve resembling the form of the blood model (shown) fit the semen data better than quadratic or straight-line regression ( $P \leq 0.001$ ). Blood and semen concentrations were significantly correlated (Pearson correlation 0.37,  $P = 0.04$ ).

**Composite Semen Model** (Figure 3). The distribution of timed semen concentrations were in excellent agreement with predictions of a semen dynamic model based on parallel dynamics with blood: the figure shows 81% of observations within one standard deviation of the predicted population mean. Moreover, 100% of observations were within a 95% prediction band. Alternative models assuming a time-shifted peak in the semen compartment were less robust.

**Dynamics of Transmission Probability** (Figure 4). Based on these predicted changes in semen concentration alone, estimated per-coital act transmission probabilities for patients with a range of set point semen RNA concentrations are 15 to 20-fold higher at peak than for the same individuals at set point. Predicted probabilities for patients with median semen concentrations:

- 1:73 coital acts at peak
- 1:1100 at set point



## CONCLUSIONS

- Our data provide evidence that acute HIV viral dynamics are approximately parallel in blood and semen.
- Our viral dynamic model suggests that individuals are hyperinfectious beginning around the onset of the acute retroviral syndrome and continuing for approximately 4 weeks.
- Susceptible partners of individuals with acute HIV infection may be at 15- to 20-fold greater risk per exposure compared to partners of individuals at virologic set point due to higher HIV shedding in semen alone.

## DISCUSSION

- Higher semen HIV viral burden is only one of many factors that may augment transmission potential for acutely infected individuals, and hence, ours may be minimum estimates of per-contact infectivity during acute infection. Other biologic factors may include differences in viral phenotype, frequent STD coinfection, and the absence of acquired mucosal immunity in regular sex partners.<sup>10</sup> Frequent partner change and riskier sex among these individuals will further amplify the impact of higher individual infectivity on epidemic spread.<sup>1</sup>
- All individuals with acute infection should be considered hyperinfectious.
- Appropriate management should include:
  - Urgent tracing of sexual contacts for prospective acute infection testing
  - Consideration of post-sexual-exposure prophylaxis
  - Consideration of early ART to reduce shedding<sup>9</sup>
- The ability to estimate the impact of measurable biologic phenomena on HIV transmission probability is a powerful tool that could be useful in modeling HIV prevention strategies.

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