PARAMETERS III:
BIOLOGY AND NATURAL HISTORY

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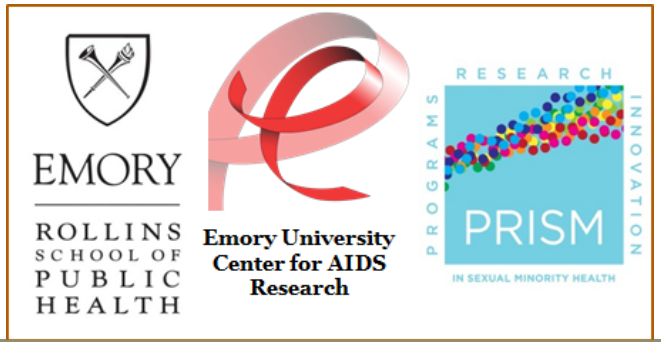


Outline for this session

- Circumcision
- CCR5-Δ32 mutation
- HIV disease progression: VL and AIDS/mortality among ART naïve

- How these and behaviors come together for per-act tx probability

- Implementing in the model

Circumcision

Circumcision: concept

- Biomedical intervention that reduces HIV acquisition risk
- Trials in sub-Saharan African heterosexual males showed ~60% efficacy
- Among MSM, marginal efficacy is lower because of varied sex roles
  - No benefit to receptive partners
  - In insertive partners…
    - Similar efficacy assumed as to heterosexuals
    - Metanalysis found insufficient evidence of efficacy in insertive MSM (Millett et al, JAMA 2008)

Circumcision: assessment and model

47. Is your penis circumcised (cut) or uncircumcised (uncut)?
Please select one choice.

circumcised

circumcised.

1 ◯ Circumcised (cut) 0 ◯ Uncircumcised (uncut) 9 ◯ Don't know

Circumcised (cut)

Uncircumcised (uncut)

?

Don't know

- 90% of both B and W men were circumcised
- Node attribute at entry. Conveys 60% protection to insertive HIV- men

CCR5-Δ32

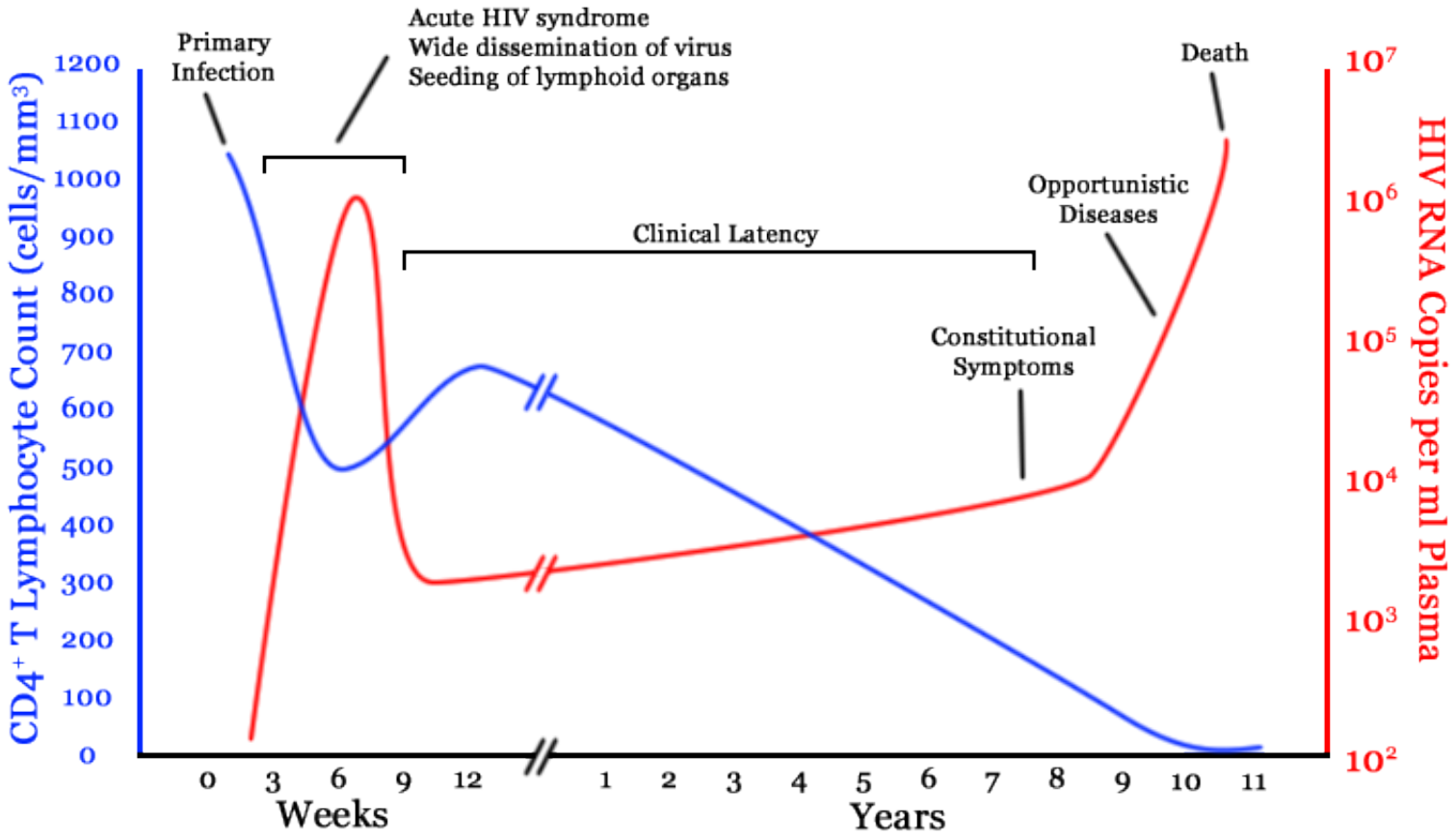
CCR5-Δ32: Concept

- Protein receptor on CD4+ T-cells that facilitates viral entry
- Δ32 mutation results in defective protein
  - Homozygote (2 copies) confers full immunity
  - Heterozygote: 70% reduced susceptibility in 1 MSM study
- Distribution of Δ32 allele different by race
  - Whites: 3.4% homozygote, 17.6% heterozygote
  - Blacks: ~0% homozygote 2.1% heterozygote

HIV disease progression: ART naïve

HIV disease progression

- HIV infection natural history, per CD4 and VL



HIV disease progression in model

- Model currently tracks VL and AIDS status (but not CD4)
- Progression to death in about 10 years:

	Duration	Start VL value	End VL value
'Up' part of curve to peak of acute virema	45 days	0	6·886 $\log_{10}$ copies per mL
'Down' part to set-point VL	45 days	6·886 $\log_{10}$ copies per mL	4·5 $\log_{10}$ copies per mL
Chronic infection	3550 days	4·5 $\log_{10}$ copies per mL	4·5 $\log_{10}$ copies per mL
AIDS to death	728 days	4·5 $\log_{10}$ copies per mL	7 $\log_{10}$ copies per mL (Death)

- Segments of VL curve are linear
- Deterministic timing. VL values too?

Bringing biology and behaviors together for HIV transmission

Bringing biology and behaviors together for HIV transmission

- Probability of HIV tx within act of serodiscordant dyad drawn as Bernoulli event with p determined by:

Predictor	Partner	Parameters	References
Sexual role (insertive or receptive)	HIV-	Receptive: 0·008938 base probability when HIV+ partner has 4·5 $\log_{10}$ viral load copies per mL	Vittinghoff[29]
		Insertive: 0·003379 base probability when HIV+ partner has 4·5 $\log_{10}$ viral load copies per mL	Vittinghoff[29]
HIV viral load (VL)	HIV+	Multiplier of $2{\cdot}45^{(VL - 4{\cdot}5)}$, where VL is expressed as $\log_{10}$ copies per mL	Wilson[30]
Acute stage	HIV+	Multiplier of 6	Leynaert,[18] Bellan[31]
CCR5 status	HIV-	Δ32 homozygote: multiplier of 0	Marmor[14]
		heterozygote: multiplier of 0·3	Marmor[14]
Condom use	Both	Multiplier of 0·25	Varghese,[32] Weller[33], Smith[34]
Circumcision status	HIV-,	Multiplier of 0·40	Gray[13]

Implementing in the model

Circumcision, CCR5

- param.mard:

```
disc.inst.B.prob = 0.445, disc.inst.W.prob = 0.691, circ.B.prob = 0.874,
circ.W.prob = 0.918, ccr5.B.prob = c(0, 0.034), ccr5.W.prob = c(0.021,
    0.176),
```

- EpiModelHIV:::setBirthAttr.mard:

```
dat$attr$circ[newIds[newB]] <- rbinom(nBirths.B, 1, dat$param$circ.B.prob)
dat$attr$circ[newIds[newW]] <- rbinom(nBirths.W, 1, dat$param$circ.W.prob)
```

```
ccr5.B.prob <- dat$param$ccr5.B.prob
ccr5.W.prob <- dat$param$ccr5.W.prob
dat$attr$ccr5[newIds[newB]] <- sample(c("WW", "DW", "DD"),
    nBirths.B, replace = TRUE, prob = c(1 - sum(ccr5.B.prob),
        ccr5.B.prob[2], ccr5.B.prob[1]))
dat$attr$ccr5[newIds[newW]] <- sample(c("WW", "DW", "DD"),
    nBirths.W, replace = TRUE, prob = c(1 - sum(ccr5.W.prob),
        ccr5.W.prob[2], ccr5.W.prob[1]))
```

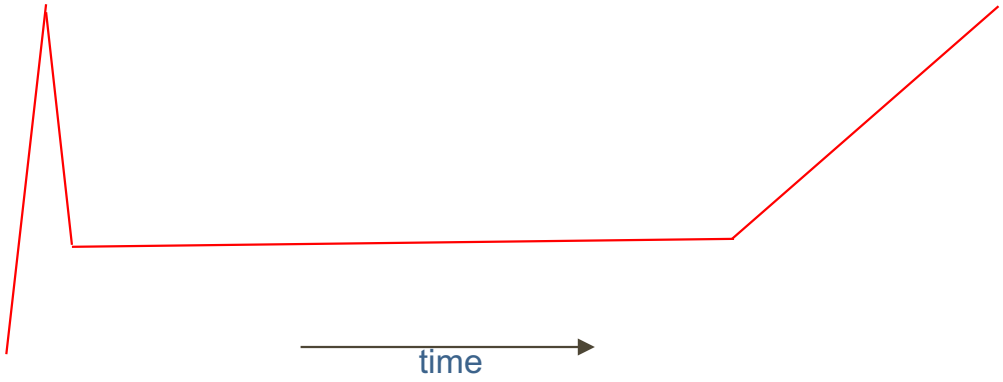
- And stay tuned for transmission….

VL and progression – ART-naive

- param.mard:

```
    7, vl.acute.rise.int = 21, vl.acute.peak = 6.886, vl.acute.fall.int = 21,
vl.set.point = 4.5, vl.aids.onset.int = 520 * 7, vl.aids.int = 52 *
    2 * 7, vl.fatal = 7, vl.full.supp = 1.5, vl.part.supp = 3.5,
```

- update.vl.mard (for viral load)
- progress.mard (for which stage)
- way too much code to show meaningfully. Summary:



- And stay tuned for transmission….

VL and progression – ART

- param.mard:

```
                                                    max.time.off.tx.full.int = 520 *
    7, max.time.on.tx.part.int = 52 * 15 * 7, max.time.off.tx.part.int = 520 *
    7, vl.acute.rise.int = 21, vl.acute.peak = 6.886, vl.acute.fall.int = 21,
```

```
    2 * 7, vl.fatal = 7, vl.full.supp = 1.5, vl.part.supp = 3.5,
full.supp.down.slope = 0.25, full.supp.up.slope = 0.25, part.supp.down.slope = 0.25,
part.supp.up.slope = 0.25, b.B.rate = 0.001/7, b.W.rate = 0.001/7,
```

- update.vl.mard: changes to viral load b/c of tx
  - summary:
    - tx makes VL go down (to different levels depending on whether full or partial suppression)
    - stopping treatment makes VL go up
    - Reinitiating tx makes VL go down again ☺

VL and progression – ART

- progress.mard: tx failure and AIDS initiation occurs when:

```
aids.tx.naive <- which(active == 1 & status == 1 & cum.time.on.tx ==
    0 & (time.since.inf >= vl.aids.onset) & stage != "D")
part.tx.score <- (cum.time.off.tx/max.time.off.tx.part) +
    (cum.time.on.tx/max.time.on.tx.part)
aids.part.escape <- which(active == 1 & cum.time.on.tx >
    0 & tt.traj == "YP" & stage == "C" & part.tx.score >=
    1 & stage != "D")
aids.off.tx.full.escape <- which(active == 1 & tx.status ==
    0 & tt.traj == "YF" & cum.time.on.tx > 0 & cum.time.off.tx >=
    max.time.off.tx.full & stage != "D")
isAIDS <- c(aids.tx.naive, aids.part.escape, aids.off.tx.full.escape)
```

- And stay tuned for transmission….

Transmission!

- param.mard:

```
birth.age = 18, b.method = "fixed", URAI.prob = 0.0082 *
    1.09, UIAI.prob = 0.0031 * 1.09, acute.rr = 4, circ.rr = 0.4,
condom.rr = 0.25, disc.outset.main.B.prob = 0.685, disc.outset.main.W
```

- trans.mard:

```
trans.ip.prob <- URAI.prob * 2.45^(ip.vl - 4.5)
trans.ip.prob[ip.stage == "AR"] <- trans.ip.prob[ip.stage ==
    "AR"] * acute.rr
trans.ip.prob[ip.stage == "AF"] <- trans.ip.prob[ip.stage ==
    "AF"] * (1 + (acute.rr - 1) * (vl.acute.fall.int - ip.stage.time[ip.stage ==
    "AF"])/vl.acute.fall.int)
trans.ip.prob[disc.ip$uai == 0] <- trans.ip.prob[disc.ip$uai ==
    0] * condom.rr
trans.ip.prob[ip.ccr5 == "DD"] <- trans.ip.prob[ip.ccr5 ==
    "DD"] * 0
trans.ip.prob[ip.ccr5 == "DW"] <- trans.ip.prob[ip.ccr5 ==
    "DW"] * ccr5.heteroz.rr
trans.ip.prob[which(ip.prep == 1 & ip.prepcl == "l")] <- trans.ip.prob[which(ip.prep ==
```

- Etc.