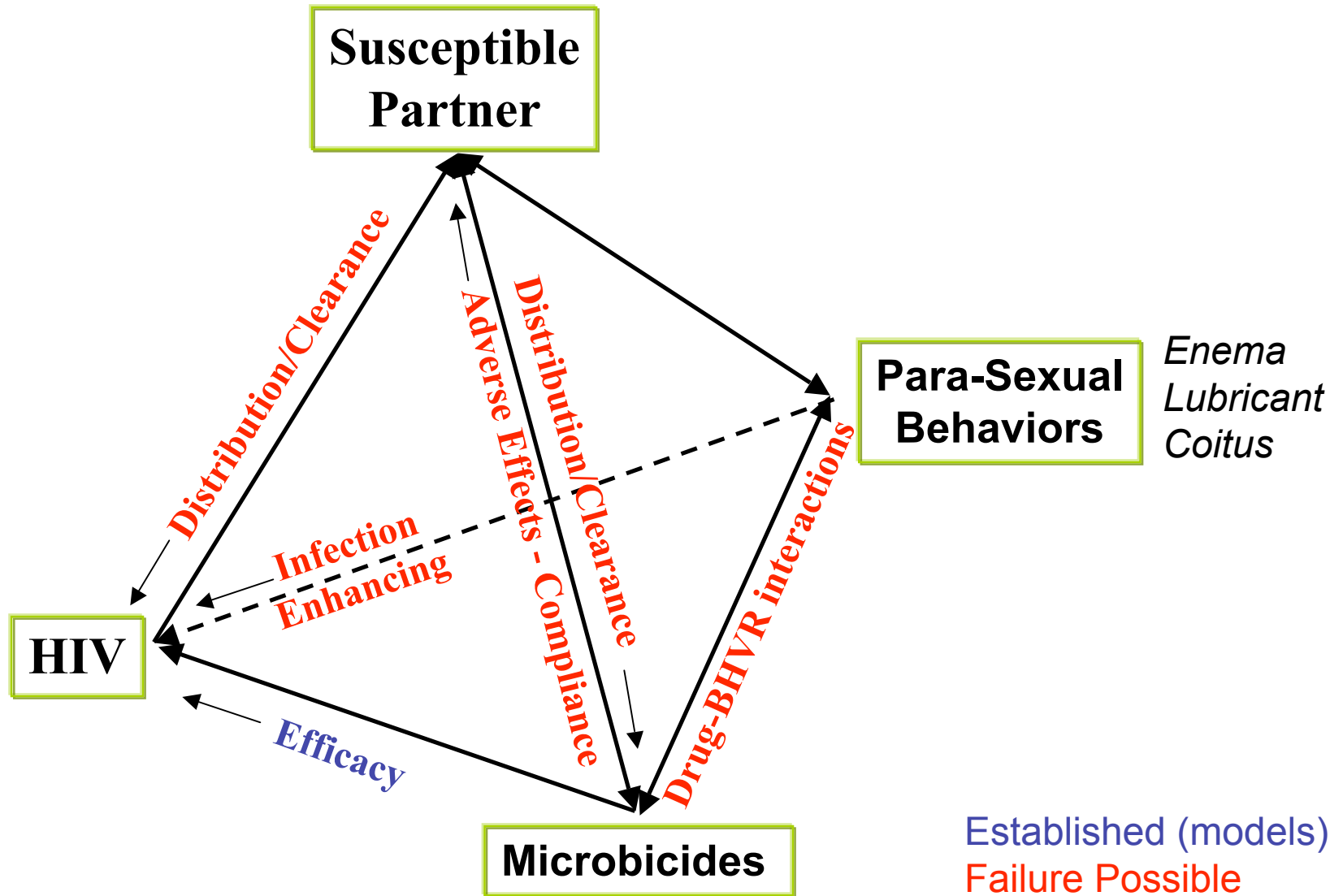


Why Microbicides Might Fail



Why Microbicides Might Fail

- Discordant HIV & microbicide distribution & clearance:
 - Luminal distribution:
 - Discordance in early minutes due to redistribution 2° coital forces
 - Liquefied seminal plasma may penetrate os & uterine cavity, unlike microbicide gel
 - Luminal Duration: persistence likely similar as factors are similar for luminal removal, but only if distribution is the same post-coitus
 - Tissue Penetration:
 - HIV gets in well enough (infection occurs), persists weeks,
 - Small molecules may not penetrate (many) and will dissipate systemically in hours
- Vaginal route not favorite of women
 - Why is oral contraception and antifungal Rx favored when vaginal alternatives exist?
 - Risk of applicators? HIV Infection? Secondary Bacterial infection?
- Parasexual Behaviors may be risky themselves & confounding in trials
 - Enema and lubricant may pose susceptibility risk to the columnar mucosa
 - Coital risk to mucosa (rectal)
- Dual Use (recto-vaginal) desired but greatly complicates development
- Rectal transmission may represent $\frac{1}{2}$ the HIV transmission risk in a population:
 - 1/10 – 1/100 women with rectal exposure on population basis
 - 10 – 100 x increased rectal transmission risk
- “Vaginal” efficacy trial may be only 50% efficacy before it starts
 - if direction followed (vaginal only), half the risk is unprotected exposure
 - If directions not followed,
 - Vagina & Rectum may be under dosed
 - Rectum exposed to product not evaluated for rectal PK and safety