8th International Conference on HIV TREATMENT AND PREVENTION ADHERENCE

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Accounting for variable adherence and sexual risk behavior patterns in the design and analysis of PrEP trials, and when modeling the impact of PrEP implementation

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New HIV prevention routes promising

- Oral and topical PrEP: mixed results
- Main explanations for variability in effects:[1]
  - Statistical chance (unlikely)
  - Biological paths (mostly unclear)
  - Non-adherence (most plausible)
- Modeling paper suggests even more complex situation[2]
- Implications possibly relevant for current discussions

1- Baeten e.a., Annu Rev Med, 2013;64:219-32; 2- de Bruin e.a, PLoS one, 2012; 7(8):e44029

Goals talk

- Explain the key concepts model paper. Steps:
  1. Factors that influence absolute risk (AR)..
  2. ..also influence on relative risk (RR) in trials..
  3. ..and the adherence - RR relationship

- Apply cumulative probability model to MB trial data:
  - True method effectiveness 50% per-contact risk reduction
  - Per-contact infection risk of .003[1] with HIV+ partner
  - Per-contact risk reduction condom use 80%[2]

- Possible implications for trial design, analyses and models

1- Boily e.a., Lancet Infect Dis, 2009;9:118-29; 2- Weller e.a., Cochrane Syst Rev, 2002: CD003255.

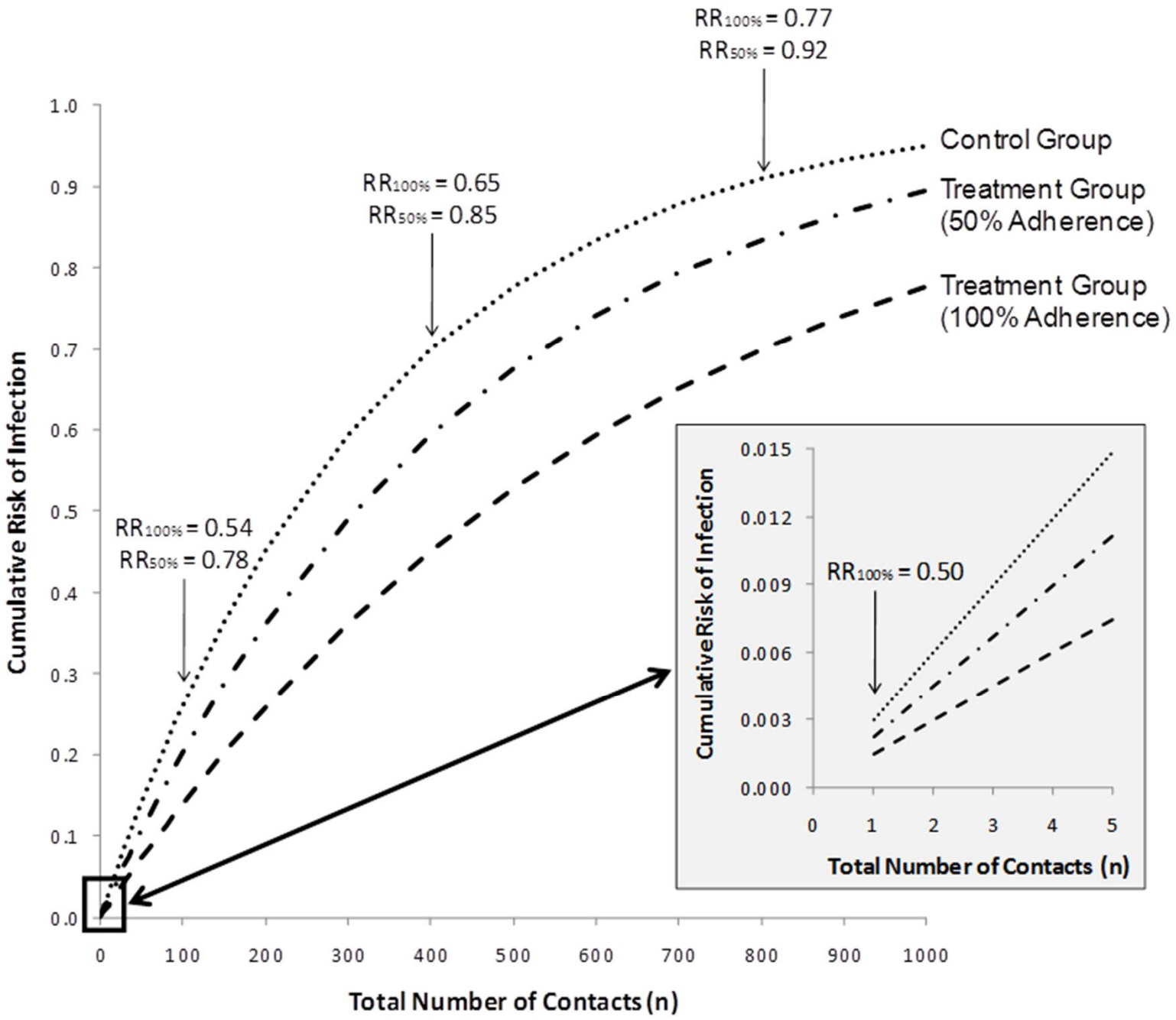
(1) Coverage = adherence percentage?

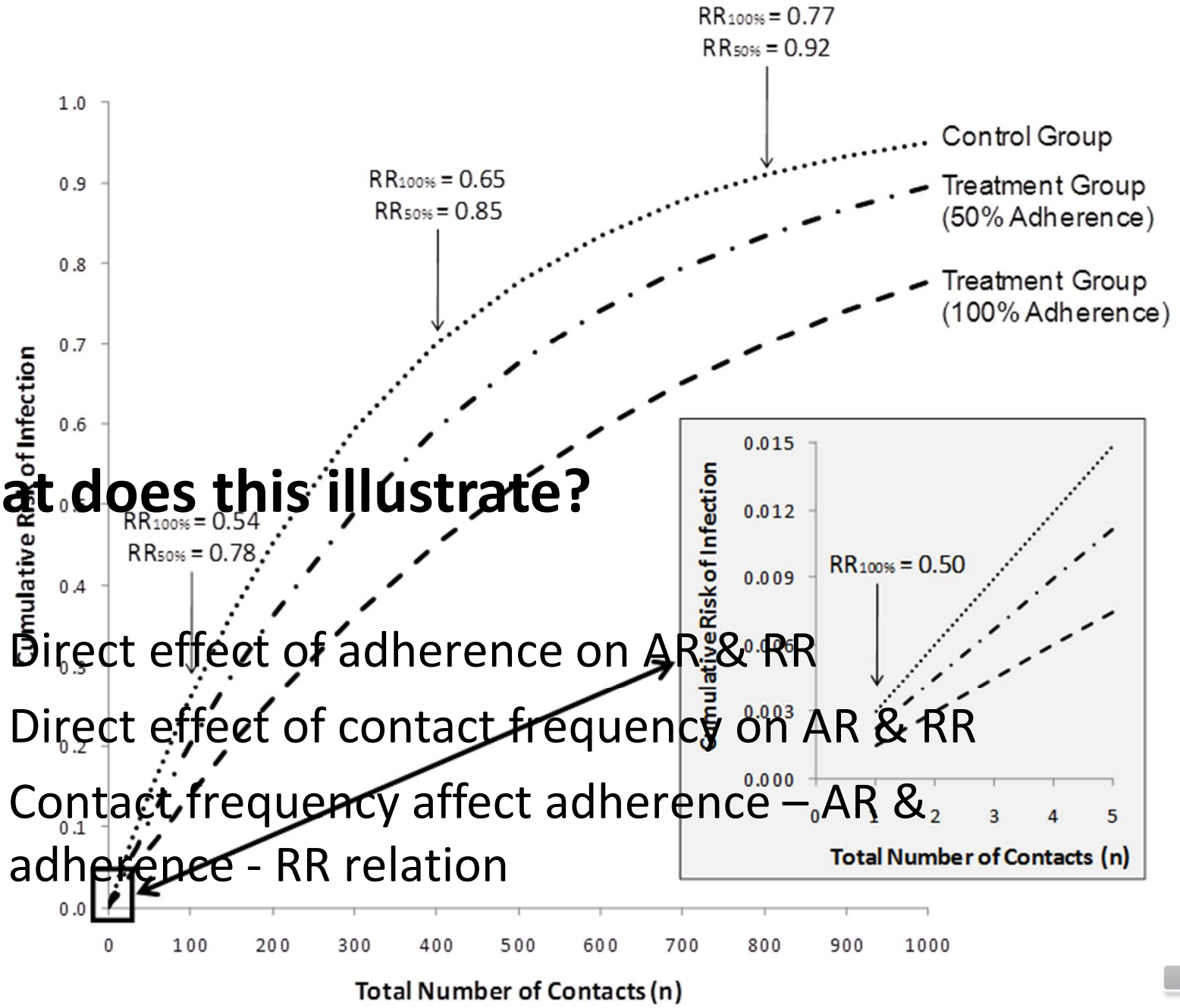
HIV treatment study:

- Adherence = (# pills taken / # pills prescribed) * 100
- 70 pills taken in 100 days for QD = 70% adherence
- Represents 30 ‘uncovered days’ (under certain assumptions)

- PrEP trial (examples for microbicide)
- Adherence = (# doses inserted / # contacts) * 100
- 70% over 100 days can be 30/100 or 3/10 ‘uncovered‘ contacts
- Control for # of contacts when predicting AR infection

- Relevant in RCTs, i.e. does it carry over to relative risk?


RR100% = 0.77
RR50% = 0.92
RR100% = 0.65
RR50% = 0.85
RR100% = 0.54
RR50% = 0.78
Control Group
Treatment Group (50% Adherence)
Treatment Group (100% Adherence)
Cumulative Risk of Infection
Total Number of Contacts (n)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
0
100
200
300
400
500
600
700
800
900
1000
RR100% = 0.50
0.000
0.003
0.006
0.009
0.012
0.015
0
1
2
3
4
5



What does this illustrate?

1. Direct effect of adherence on AR & RR
2. Direct effect of contact frequency on AR & RR
3. Contact frequency affect adherence – AR & adherence - RR relation

(2) Riskiness of the contact

- Evident that riskiness of a contact influences AR
  - Vaginal/anal, STD, treatment coverage area, condom use
- Riskiness effect on RR and adherence-RR relation?

Number contacts	Adh 50%, no condom	Adh 50%, condom	Adh 100%, no condom	Adh 100%, condom	Ratio 50/100 no condom	Ratio 50/100 condom
400	0.85	0.77	0.65	0.53	1.31	1.45

- Separate adherence % for high-risk & low-risk encounters

(3) Number of partners

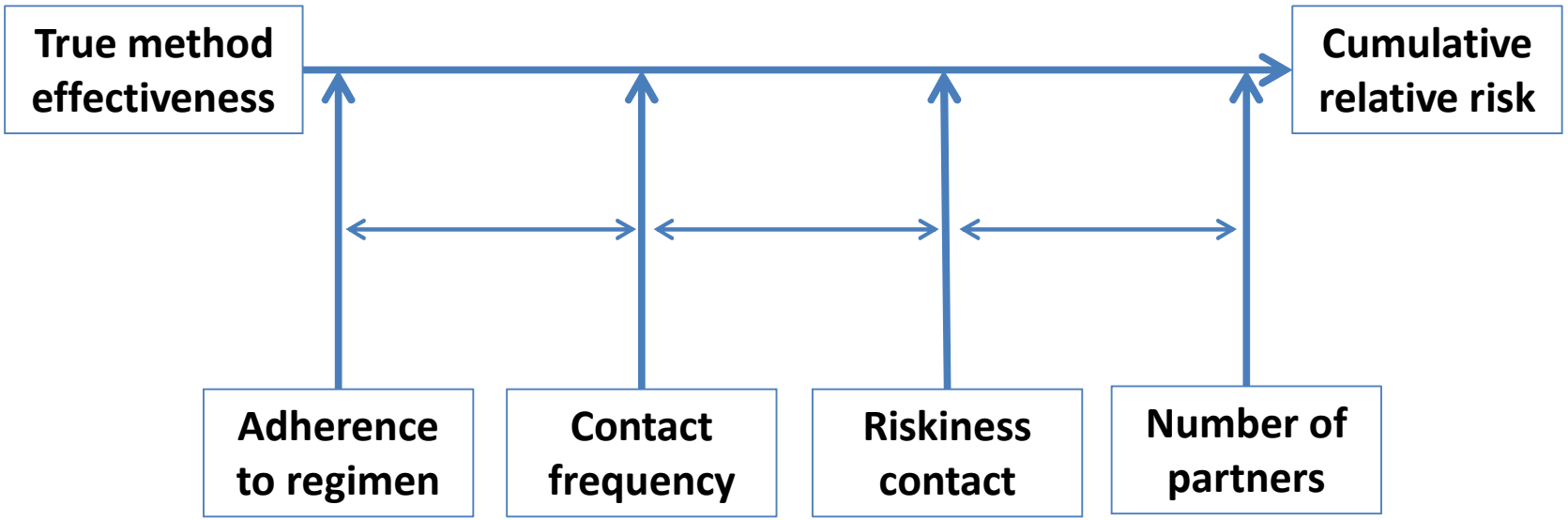
Å In real life not a single partner, and the more partners, the larger the probability of contact with an HIV+ partner

	Control	AR + Adh 50%	AR + Adh 100%	RR+ Adh 50%	RR + Adh 100%	Ratio 50/ 100%
1p * 400c	0.14	0.12	0.09	0.65	0.85	1.31
10p * 40c	0.21	0.16	0.11	0.54	0.78	1.44

p = partner * c = contacts = 400

Å AR, RR and adherence–RR relation depends on # partners

All these factors simultaneously..



- …influence absolute and relative risks
- …influence the relationship adherence → relative risk
- …obscure the true method effectiveness (TME) in trials

Implications and illustrations

- Role of (dominant) sexual behavior patterns:
  1. Abdool Karim: few contacts, few partners, high condom
  2. Skoler-Karpoff: more frequent, less condom use
  3. Feldblum: more frequent & partners, high condom use

- Role of single vs high-risk & low-risk adherence rates

- Caprisa parameters as in de Bruin e.a. (2012)[1]

1- de Bruin e.a, PLoS one, 2012; 7(8):e44029

Trial design implications

- Trial power for different sexual risk behavior patterns

Study	Probability control	Probability intervention	Cumulative RR	Required sample size/arm
1	0,134	0,085	0,634	669
2	0,247	0,195	0,789	1034
3	0,620	0,418	0,674	101

- Dito for general vs separate adherence % high & low risk
- Implication 1: Consider effect modifiers in sample size computations and update based on actual participant behavior
- Implication 2: Accurately measure all relevant variables and patterns (e.g. adherence high-low risk encounters)

Trial analysis implications

- RR is a unique product of trial behavior * time * TME (*other)
- TME can be compared and used as input for (CE) models
- Implication 3: In order to identify the true treatment effect, primary trial analyses may have to control for effect modifiers (not just overall adherence)
- Effect differential adherence on TME conclusions, Caprisa
  - 70% vs. 78% low & 44% high risk (1.8 times lower adherence)
  - TME estimate 57% versus 68%

Implications for (CE) models

- Modest changes in parameters can have large influence on projections (e.g. TME 67% or 58%)
- (CE) Models advanced[1] but assume general adherence percentage:
  - 61% overall: 580 infections prevented
  - 78% low vs 44% high risk (average 61%): 460 prevented (21% pts less)
- Implication 4: (CE) models require accurate TME estimates and actual population behavior estimates (e.g, adherence, condom use, etc)
- Implication 5: (CE) models may need to differentiate between adherence levels at high vs low risk encounters

1- Gomes e.a., PLoS Med, 2013;10(3):e1001401

Conclusion & limitations

- Conclusions:
  - Trial design, analyses and modeling studies could benefit from considering the influences described
- Future research:
  - Empirically test model-based assumptions
  - Improve measures and obtain accurate population data
- Limitations:
  - Illustrations based on average trial data
  - Scenario's somewhat different for oral versus topical
  - Not all relevant variables included, e.g. frailty[1]

1- O'Hagan e.a., AIDS, 2012;26(2):123-6

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de Bruin & Viechtbauer, PLoS one, 2012; 7(8):e44029

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