HPTN
HIV Prevention
Trials Network

Primary analysis methods

HPTN 071 (PopART)

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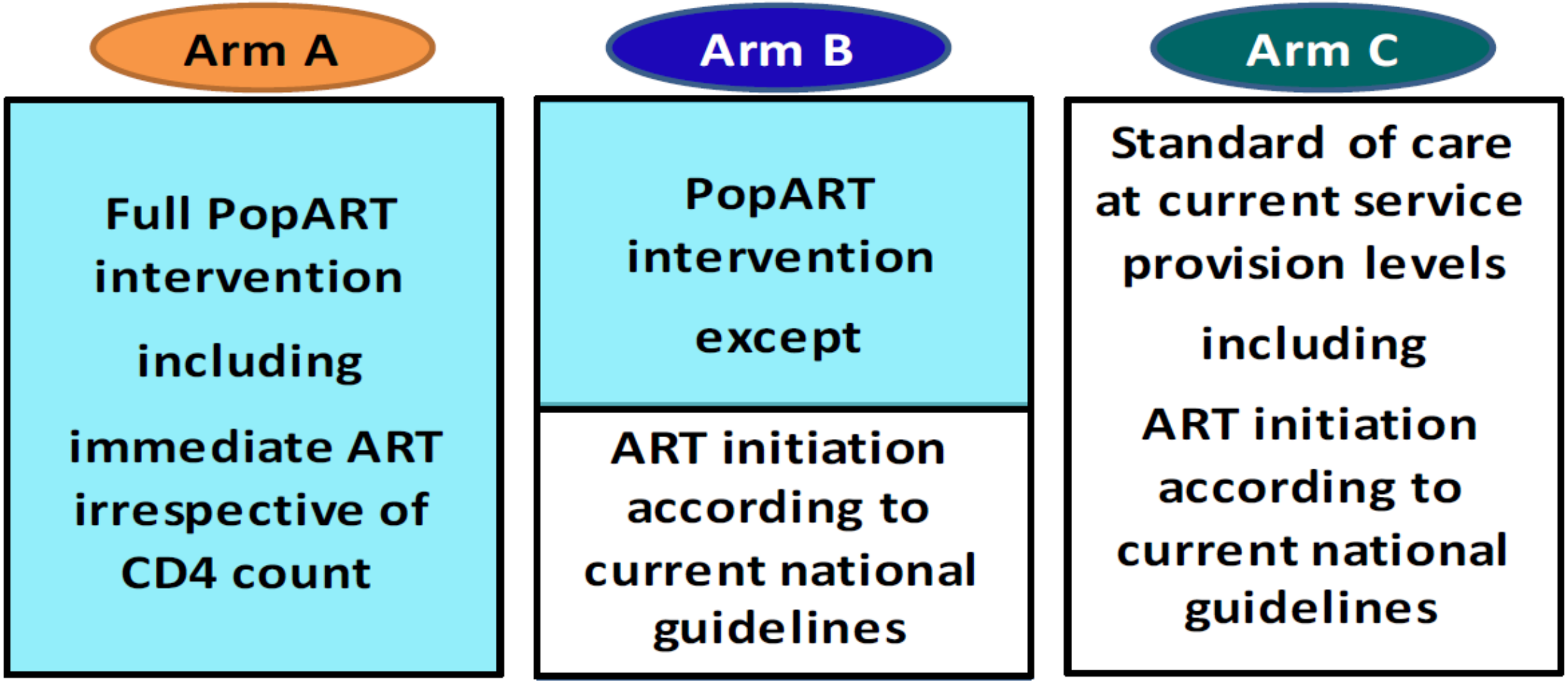
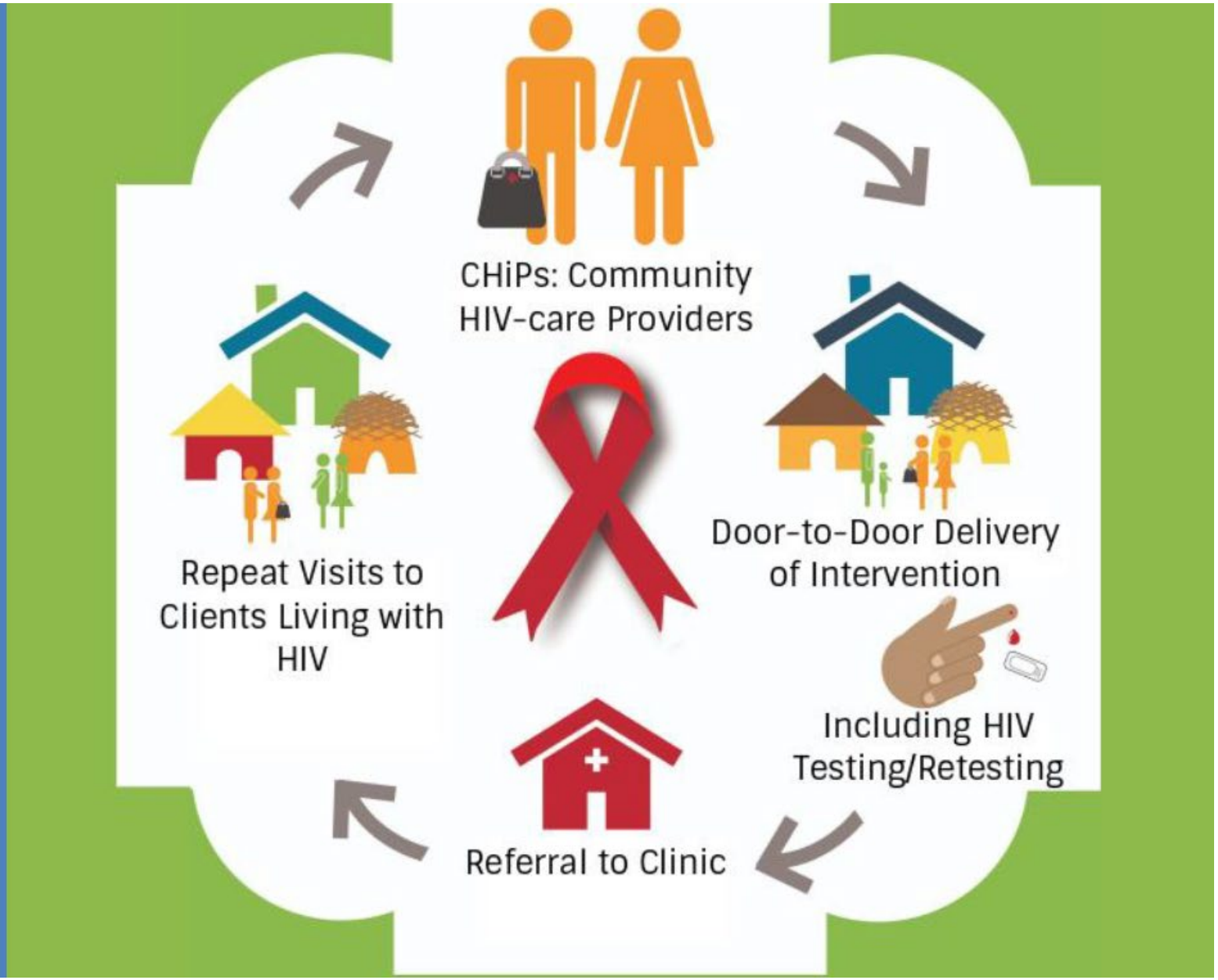
Intervention Arms



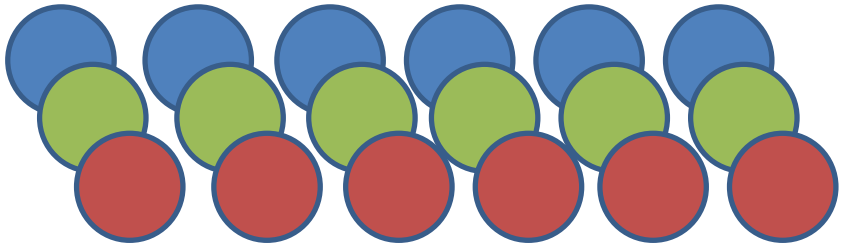
PopART Intervention

CHiPs Door-To-Door Intervention

- Universal HIV counselling and testing
- VMMC referral
- PMTCT referral
- STI screening
- TB screening
- Condoms

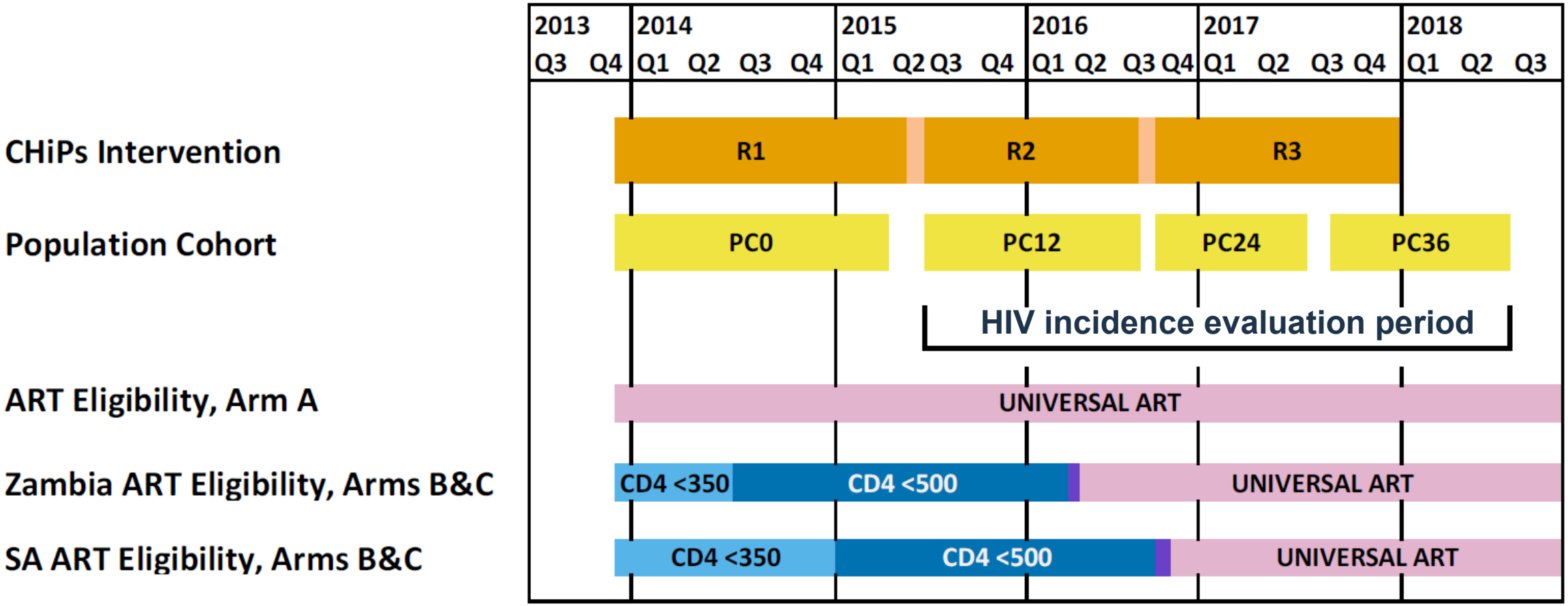


Study Design



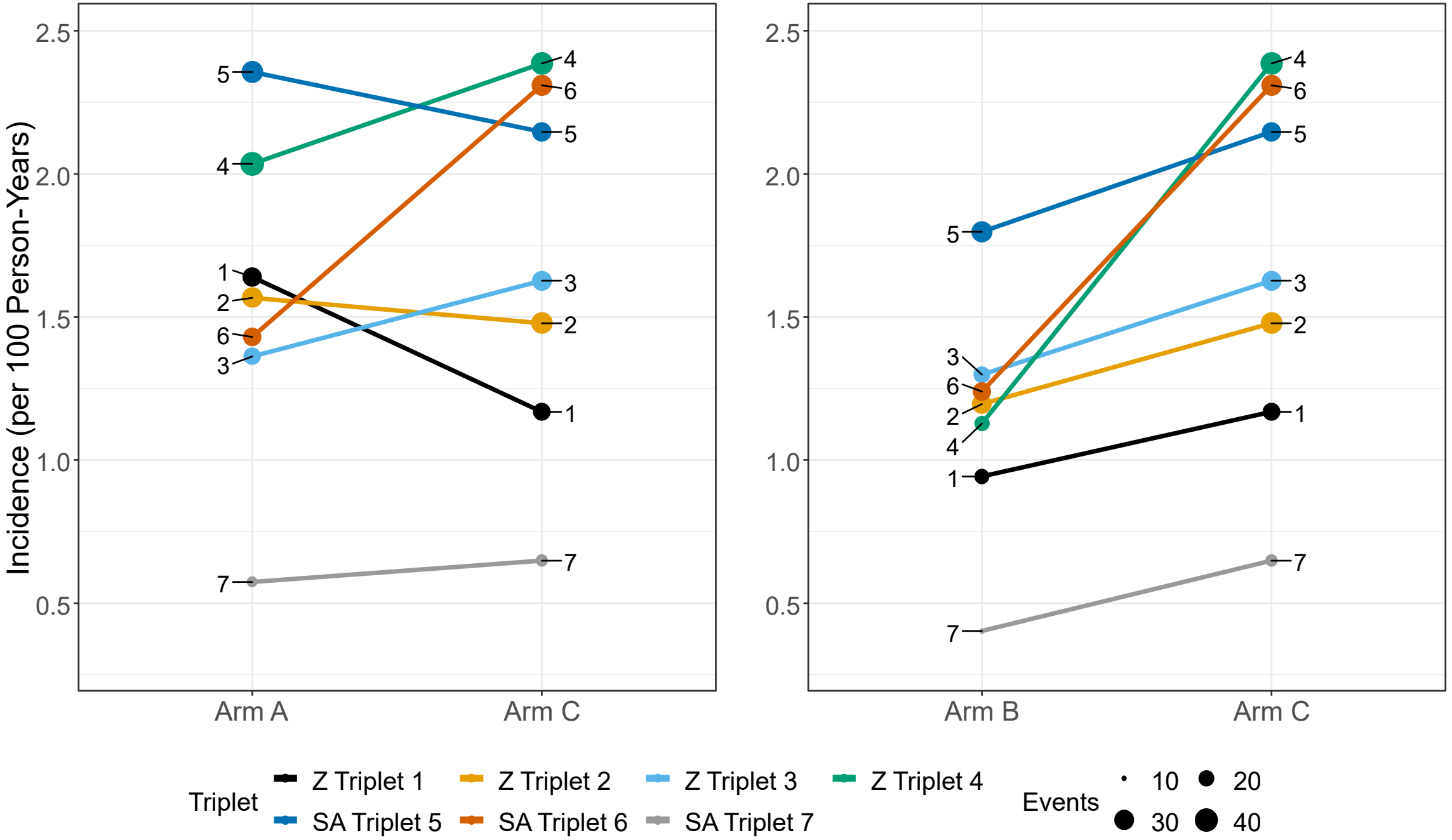
- Cluster Randomized Trial:
  - 21 Communities randomized to 3 arms using a matched triplets design (7 triplets)
- Impact of the intervention measured in the Population Cohort (PC)
  - 2000 participants selected at random within each communities
  - Visits to participants completed each year (PC0, PC12, PC24, PC36)
- Intervention and randomization in the trial is *community level*, although HIV incidence is measured in population cohort *participants*.
  - How do analysis methods account for this multi-level design?

Study Timeline



Primary Outcome

- HIV Incidence (PC12-PC36)
- Compare: Arms A (Full PopART) and B (CHiPs + SoC ART) with C (SOC)
- Analytic features
  - Two stage analysis method for matched cluster-randomized trials
  - Age changing over time
  - Imputation of infection status for seroconverters not seen at PC12


Incidence (per 100 Person-Years)
2.5
2.0
1.5
1.0
0.5
Arm A
Arm C
Arm B
Arm C
Triplet
Z Triplet 1
Z Triplet 2
Z Triplet 3
Z Triplet 4
SA Triplet 5
SA Triplet 6
SA Triplet 7
Events
10
20
30
40

Two-Stage Incidence Analysis Method

- Stage 1: Individual-level to community-level summary

  Account for differences in community HIV incidence predicted by age, gender and baseline community HIV prevalence

- Stage 2: Analysis of community summaries

  Account for triplets

Two-Stage Incidence Analysis Method

- Stage 1: Individual-level to community-level summary

  Account for differences in community HIV incidence predicted by age, gender and baseline community HIV prevalence

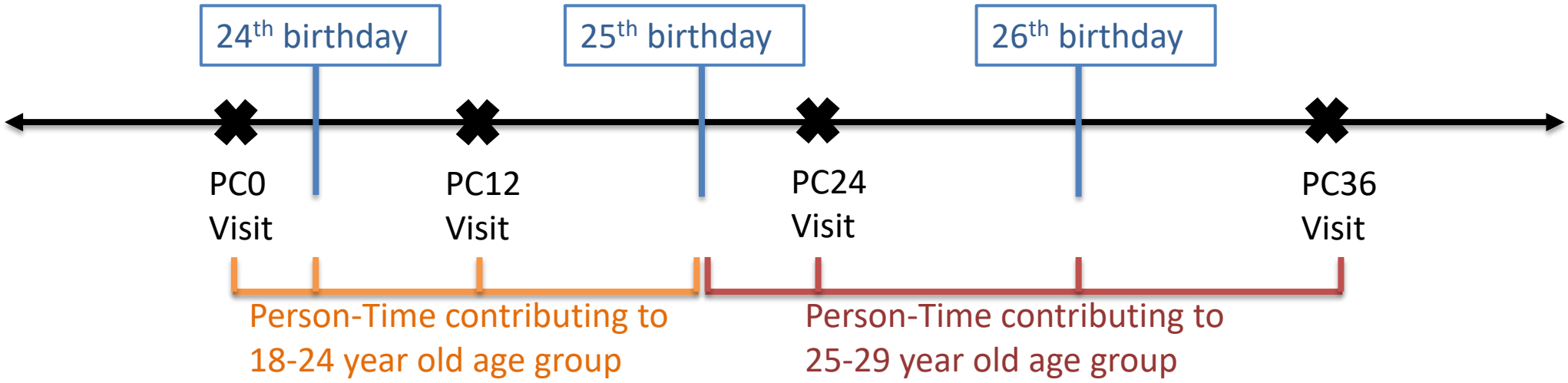
  What value of age do we use for individuals ?

- Stage 2: Analysis of community summaries

  Account for Triplets

Nuance of Age in Incidence Analyses

- Age is a known predictor of HIV incidence, and ***participant age changes*** throughout the 4 years of the study.
- Using visit dates and birth dates, each year is split into "age-level" data for participants in the incidence analyses (Lexis expansion).
- Each participant can contribute person-time in different age groups.



Two-Stage Incidence Analysis Method

- Stage 1: Individual-level to community-level summary

  Account for differences in community HIV incidence predicted by age, gender and baseline community HIV prevalence

  1. Predict the number of events "expected" in that community, E_{ij}

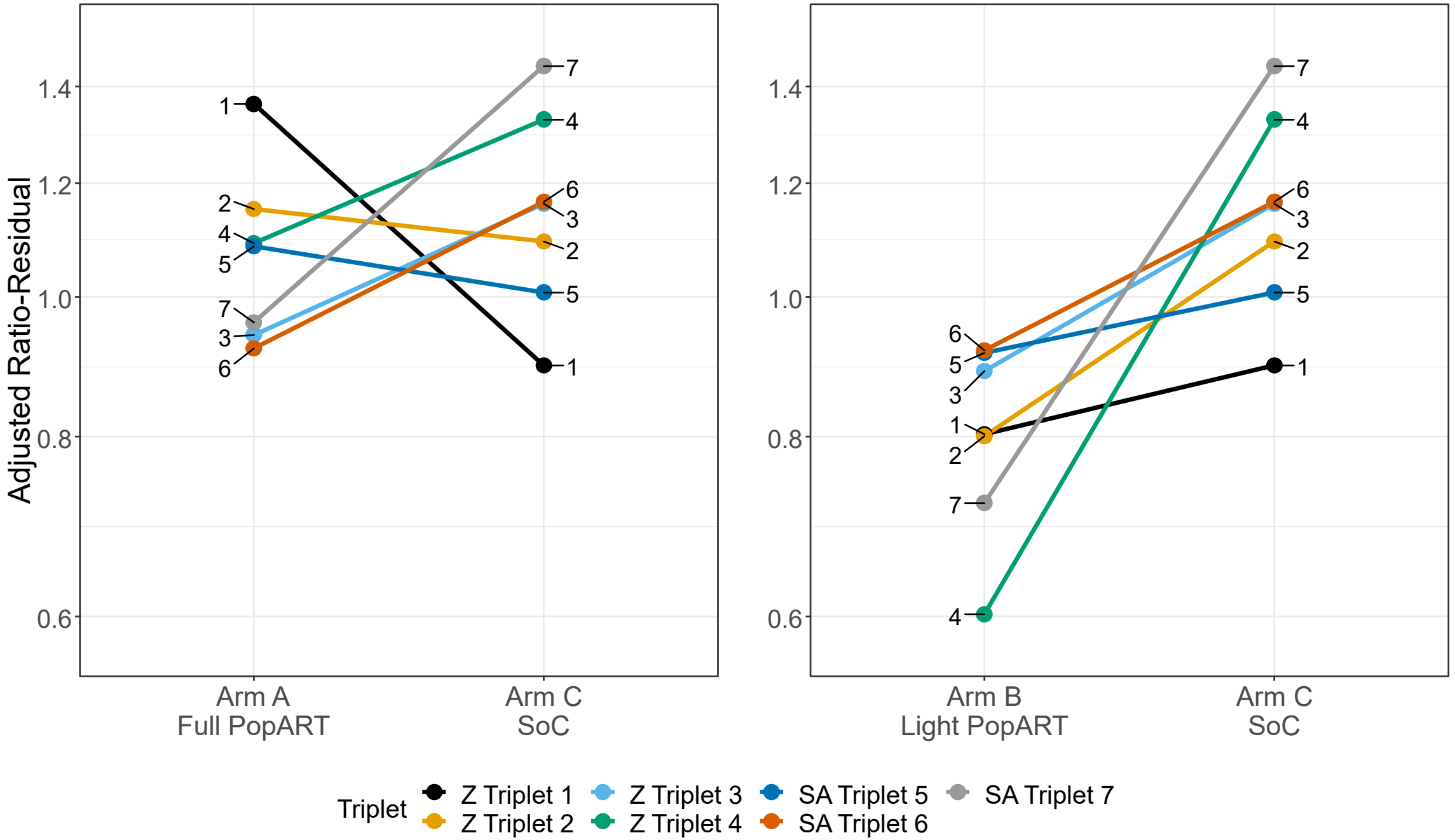
     Use Poisson regression to predict HIV infection using individual (changing) age and sex, community HIV prevalence (*but not arm*).

  2. Community summary: ratio of observed to predicted number of HIV infections

$$R_{ij} = \frac{O_{ij}}{E_{ij}} = \text{"adjusted ratio-residual"} \begin{cases} < 1 & \text{More observed than expected} \\ > 1 & \text{Fewer observed than expected} \end{cases}$$

- Stage 2: Analysis of community summaries

  Account for triplets


Adjusted Ratio-Residual
1.4
1.2
1.0
0.8
0.6
Arm A
Full PopART
Arm C
SoC
Arm B
Light PopART
Triplet
Z Triplet 1
Z Triplet 2
Z Triplet 3
Z Triplet 4
SA Triplet 5
SA Triplet 6
SA Triplet 7

Two-Stage Incidence Analysis Method

- Stage 1: Individual-level to community-level summary

  Account for differences in community HIV incidence predicted by age, gender and baseline community HIV prevalence

  1. Predict the number of events "expected" in that community , E_{ij}
     - Use a Poisson regression for HIV infection using HIV prevalence, age and sex (BUT NOT ARM). Account for person-years of observation.
  2. Community summary: ratio of observed to predicted number of events

$$R_{ij} = \frac{O_{ij}}{E_{ij}}$$ - "adjusted ratio-residual" $\begin{cases} < 1 & \text{More observed than expected} \\ > 1 & \text{Fewer observed than expected} \end{cases}$

- Stage 2: Analysis of community summaries

  Account for triplets

  - Perform a two-way ANOVA on log adjusted ratio-residuals, using Arm and Triplet in the model.
  - t-test used to assess for differences between Arms.

Missing HIV serostatus at PC12

- Primary HIV incidence: Seroconversion between PC12 and PC36

	PC0	PC12	PC24	PC36	Seroconverters	Person Years
Complete case	✓	✓	✓	✓	505	36160
Missing PC12	✓	×	✓	✓	67	4833
Missing PC12 and PC24	✓	×	×	✓	57	3355

- In primary analysis
  - Number of seroconverters omitted ~ 55
  - Number of person-years lost ~ 3,600.
- Approximately 10% of person-years omitted due to missed visits
- ***Use imputation to include the information from these cases***

Imputation method

Seronegative before and after missed visit(s)

Individual	PC0	PC12	PC24	PC36
Complete case	Neg	Neg	.	Neg
Missing PC12	Neg	.	.	Neg
Missing PC12 and PC24	Neg	.	Neg	Neg

Imputation method

Seronegative before and after missed visit(s)

Individual	PC0	PC12	PC24	PC36
Complete case	Neg	Neg	**Neg**	Neg
Missing PC12	Neg	**Neg**	**Neg**	Neg
Missing PC12 and PC24	Neg	**Neg**	Neg	Neg

Imputation Methods

Individual	PC0 Status	PC12 Status	PC24 Status	PC36 Status
Missing PC12	Neg	.	Pos	Pos
Missing PC12 and PC24	Neg	.	.	Pos

Hot deck imputation

- Randomly select from **complete case data of seroconverters** matched for sex and community ("donors")

Imputation Methods

- Seroconverter with missing PC12 visit

Sex	Community	PC0 Status	PC12 Status	PC24 Status	PC36 Status
Male	5	Neg	.	Pos	Pos

- Complete case donors:

Sex	Community	PC0 Status	PC12 Status	PC24 Status	PC36 Status
Male	5	Neg	Pos	Pos	Pos
Male	5	Neg	Neg	Pos	Pos
Male	5	Neg	Neg	Pos	.
Male	5	Neg	Neg	Pos	.
Male	5	Neg	Pos	Pos	Pos

Imputation Methods

- Seroconverter with missing PC12 visit

Sex	Community	PC0 Status	PC12 Status	PC24 Status	PC36 Status
Male	5	Neg	Neg	Pos	Pos

- Complete cases donors:

Sex	Community	PC0 Status	PC12 Status	PC24 Status	PC36 Status
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Male	5	Neg	Neg	Pos	.
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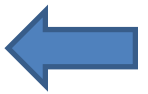

Random selection

Imputation Methods

- Seroconverter with missing PC12 visit

Sex	Community	PC0 Status	PC12 Status	PC24 Status	PC36 Status
Male	5	Neg	Pos	Pos	Pos

- Complete cases donors:

Sex	Community	PC0 Status	PC12 Status	PC24 Status	PC36 Status
Male	5	Neg	Pos	Pos	Pos
Male	5	Neg	Neg	Pos	Pos
Male	5	Neg	Neg	Pos	.
Male	5	Neg	Neg	Pos	.
Male	5	Neg	Pos	Pos	Pos

Random selection

Imputation Analysis

- Compute 20 imputation data sets, with every individual with missing HIV PC12 status imputed (no missing PC12 HIV status)
- For each of the 20 imputation datasets, perform the two-stage analysis and get estimate of intervention effect
- Intervention point estimate: mean of 20 effect estimates.
- Variance estimate: combines within and between variation from the imputation estimates
- Perform t-tests using imputation estimate and imputation variance.

PC12-PC36 Incidence Results

	Arm A Full PopART	Arm B CHiPs + SoC ART	Arm C SoC	Overall
HIV Incidence Complete Cases	180 / 11,998 (1.42%)	140 / 12,780 (1.06%)	185 / 11,382 (1.60%)	505/36,160
HIV Incidence With Imputation	198 / 12,990 (1.45%)	157 / 14,149 (1.06%)	198 / 12,563 (1.55%)	554/39,702 +49/+3,542

* Incidence % is the geometric mean of community mean incidence.

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HIV Incidence With Imputation	198 / 12,990 (1.45%)	157 / 14,149 (1.06%)	198 / 12,563 (1.55%)	554/39702 +49/+3,542
Adjusted Rate Ratio (95% CI)	0.93 (0.74, 1.18)	0.70 (0.55, 0.88)		
	7% Reduction	30% Reduction		
P-value	0.51	0.006		

* Incidence % is the geometric mean of community mean incidence.

Conclusion

- Analysis of cluster randomized trials based on the design
  - Matched triplets
  - Cluster aggregated summaries
- Even when the analysis is straightforward, attention to details and exceptions are important

Thanks to SCHARP Colleagues

- Tim Skalland
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