Using Cross-sectional Recency Assays to Assess Prevention Efficacy: Future Trial Design and Sample Size Considerations

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Cross-sectional Incidence Estimation

- To infer incidence based on a cross-sectional sample.

- Apply recency assay to HIV-positive subjects to detect recent infections.
  - e.g., LAg avidity assay + Viral Load

Cross-sectional Incidence Estimation

- In a cross-sectional sample
  - N_-: number of HIV-negative subjects
  - N_+ : number of HIV-positive subjects
  - N_{rec} : number of test-recent subjects

- Incidence can be estimated by

$$\frac{N_{rec}}{N_- \times MDRI}$$

  - MDRI (mean duration of infection): the mean duration of test-recent for an HIV-positive subject.

Cross-sectional Incidence Estimation

- To correct for false recency (test-recent for long-infected subject), a modified estimator

$$\frac{N_{rec} - FRR \times N_{+}}{N_{-} \times (MDRI - FRR * T)}$$

  - T: cutoff for long-infected subject (T=2 years)
  - MDRI (mean duration of infection): the mean duration of test-recent for an HIV-positive subject infected less than T.
  - FRR (false-recent rate): the probability of test-recent for a long-infected subject.

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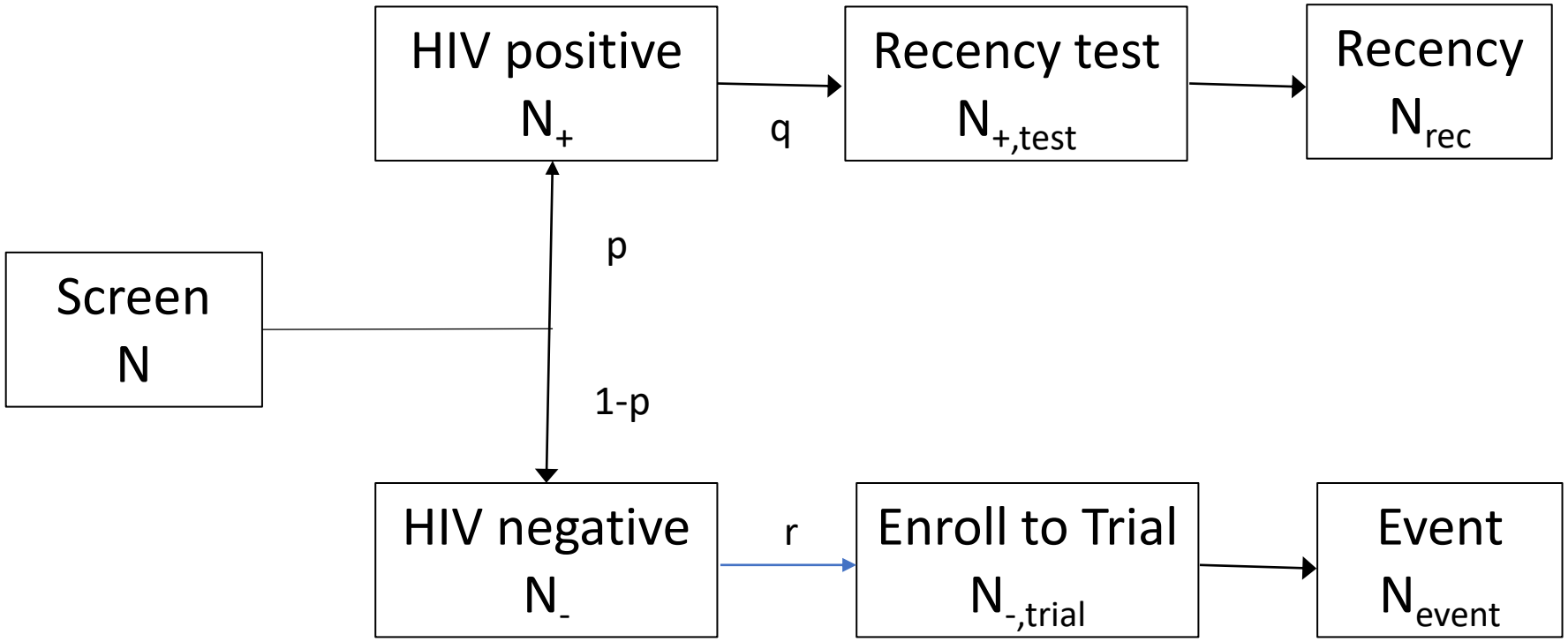
Cross-sectional Incidence Estimation as Counterfactual Placebo

- Make use of the **screening population**, which can be viewed as similar to the trial population, except for HIV status and other inclusion/exclusion criteria.
- Apply recency assay to samples collected at **screening**.
- Estimate counterfactual placebo HIV incidence rate by cross-sectional incidence estimator.

Study design



Placebo (P)

Experimental (E)

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Hypothesis Testing

$$H_o: \frac{E}{P} = R_0 \qquad H_a: \frac{E}{P} \neq R_0$$

- Form a Z-statistic for E/P
- Reject H_o if $|Z| < z$
- $P(|Z| < z\,|H_o) = \alpha$
- $P(|Z| < z|H_a) = \beta$ for a specific H_a

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Sample Size

The following design parameters must be specified for any given trial.

- **Expected placebo incidence rate**
- Recency test characteristics (FRR, MDRI, T, relative SE's)
- Other design parameters (p, q, r, followup time)
- **Type 1 error α and incidence ratio under H_o - R_0**
- **Desired power β under H_a - R_1**

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$$H_o: \frac{E}{P} = 0.5 \quad \Rightarrow \quad H_a: \frac{E}{P} = 0.2$$

Sample size is the number of persons screened.
Assumptions: 90% of HIV negative individuals enroll on PrEP, 90% of HIV positive specimens yield valid recency testing results, two years of follow-up on PrEP, 7% RSE on the MDRI, 25% RSE on FRR, significance level 0.05 (two-sided) and 80% power.

	US MSM
Incidence	3.42%/yr
Prevalence	14.5%
subtype	B
MDRI (days)	142
FRR	1.0%
Sample size	2,190

Expected Numbers under H_a

Recency Test		Experimental Product Trial	
# Tested	# Test-recent	# Enrolled	# Events
286	24	1685	23

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Conclusions

- We have proposed a study design for active-arm trial with counterfactual placebo based on cross-sectional incidence with recency assay.
- The approach is feasible in terms of calculated total screening sample size.
- Other operational issues.
- Extension to active-control trial.

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