BALANCING STATISTICAL POWER AND RISK IN HIV CURE CLINICAL TRIAL DESIGN

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Background:
Analytical treatment interruptions (ATI) are closely monitored, temporary pauses of antiretroviral therapy (ART) in the context of an HIV cure clinical trial. They are currently the gold standard in determining if the intervention being tested can achieve sustained virological control in the absence ART. However, withholding ART comes with risks and discomforts to the trial participant including rebound viremia, and frequent blood sampling. We used mathematical models to explore how ATI study design can be improved to maximise statistical power, while minimising risks to participants.

Methods:
Using previously observed dynamics of time to viral rebound (TVR) post ATI, we modelled estimates for optimal sample size, timing of sampling and duration to follow up required to detect a significant difference in the time to detection of virus between control and intervention groups. Control and intervention groups were compared using a log-rank test, and analytical and stochastic techniques.

Results:
In placebo-controlled TVR studies, 120 participants are required in each arm to detect a 30% difference in the size of the viral reservoir at 80% power **(Fig1A).** Using historical controls instead of placebo arms could reduce the number of participants required to test the intervention **(Fig1B)**. Regardless of sample size, there was little statistical advantage to measuring viral load more frequently than weekly **(Fig1C)**, or interrupting ART beyond 5 weeks **(Fig1D)**. **Fig1E** demonstrates that a 5-week ATI study with weekly viral load monitoring is almost identical in terms of statistical power compared to continuous monitoring for an indefinite period.

Conclusion:
We propose that mathematical models can be used to improve ATI trial design. Most recent HIV cure trials are underpowered to detect changes in the viral reservoir. TVR studies can be shortened to 5 weeks with weekly viral load monitoring while maintaining statistical power. This has implications on future ATI trial development.

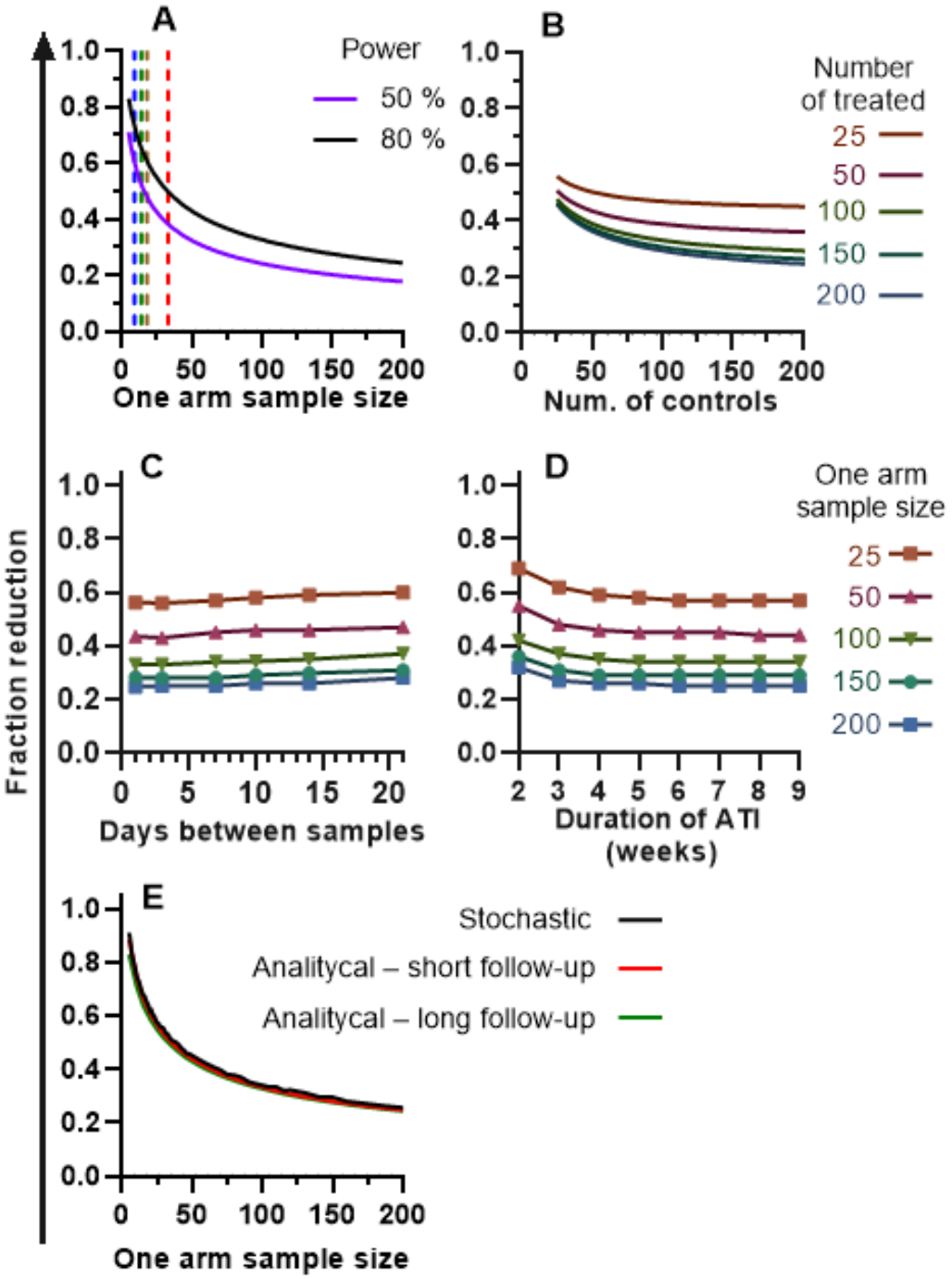

Figure 1. Detectable reduction of the rate of virus rebound using time-to-detection method in a model of a controlled study.
A) Number of participants in a single arm needed to detect a given reduction in reactivation rate with power of both 80% and 50%. B) Reduction in reactivation rate that could be detected with 80% power, given a treatment group size of 25, 50, 100, 150 and 200 participants and variable number of historical controls.C and D) The effect of frequency of sampling and duration of ATI on detecting a reduction in reactivation rate with 80% power. E) Short-course ATI with weekly sampling maintains statistical power (80%). The green curve shows the analytical relationship that assumes continuous detection of reactivation and a long time window (all

participants are detected). Red curve shows the analytical relationship corrected for the number of participants that are expected to be detected within 5 weeks of stopping ART. Black curve shows a stochastic simulation assuming weekly sampling and 5 weeks ATI.

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