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Longer-Term Follow-Up for STEP/HVTN 502

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The Issues

- Uncertainty remains about the possibility of increased risk of HIV acquisition among some participants who received vaccine. How can we best resolve this uncertainty?
- STEP study participants have made an important contribution – how can we maximize their contribution?
- The highest priorities are
 - Participant well-being
 - Obtaining reliable data



Framing the Issue

- What can we do to resolve the uncertainty we have about whether the vaccine caused an increased risk of acquisition in any specific subgroups?
- If there is a risk,
 - Can we identify factors associated with this risk?
 - Can we define how long it lasts?
 - On an individual level, can we identify any co-factors that would reduce this risk over time?
- What is the best way to address these questions?



Obtain More Information

- Analysis is ongoing of already-collected data and specimens
- Because almost all participants in STEP had received 3 vaccinations, we can learn much more by continued follow-up of these participants
- A variety of potential approaches to the longer-term follow-up portion of STEP. What is the best design?



Potential Objectives of Longer-Term Follow-Up

- **Objective 1:** Closely monitor STEP participants for risk for HIV acquisition
 - Monitor HIV infection rates over time
 - Continue to provide client-centered HIV risk reduction counseling, HIV testing, and linkage to local prevention services at regular intervals
 - Participants may also come in for off-schedule counseling, HIV testing, and/or referrals
 - Close follow-up allows timely identification of HIV infection
 - All HIV infected participants are provided linkage to local medical and psychosocial services, and have access to antiretroviral therapy, when needed



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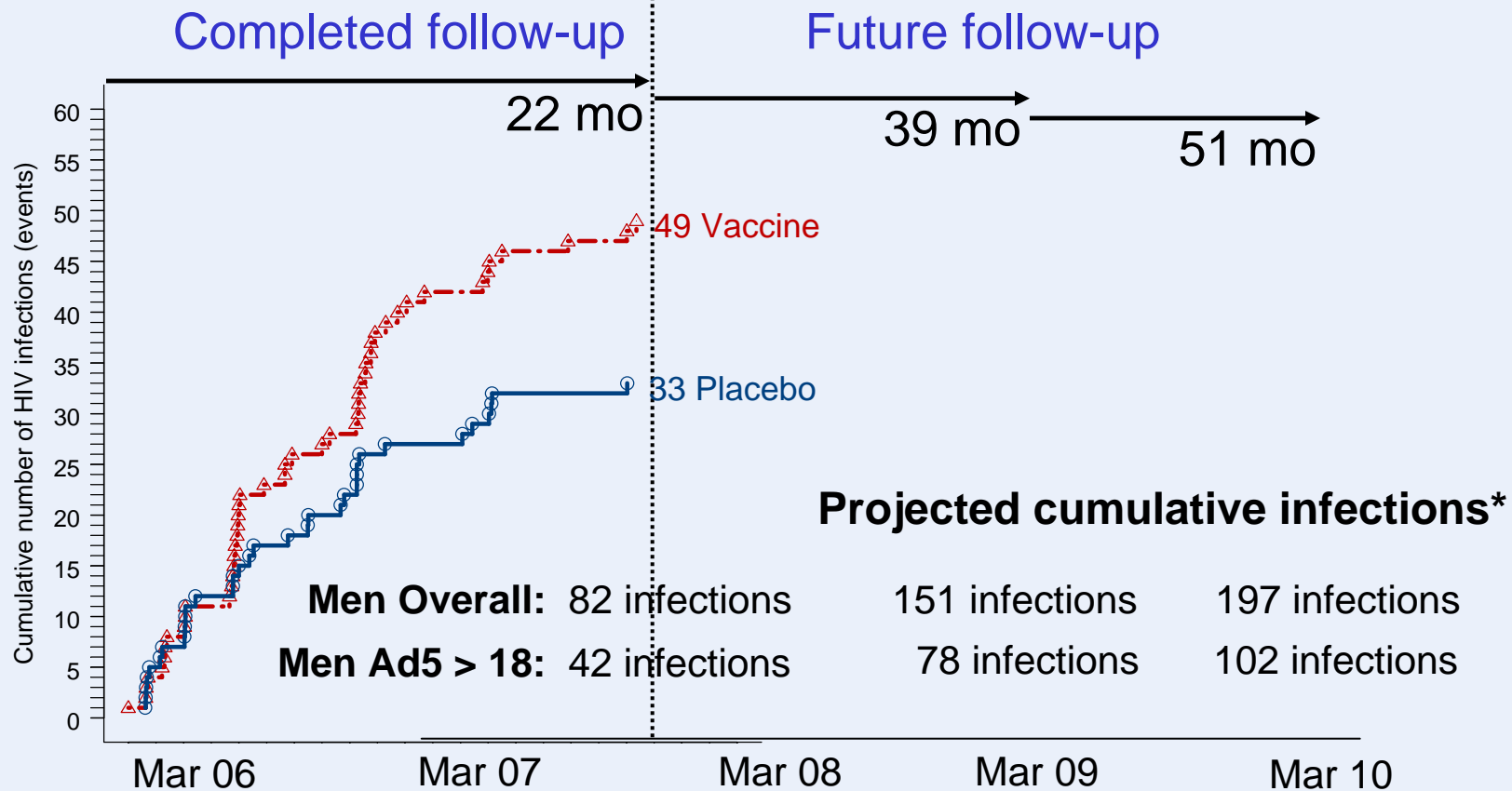
Potential Objectives of Longer-Term Follow-Up

- **Objective 2:** Evaluate the **relative risk (RR)** of HIV acquisition for vaccine compared to placebo recipients over the next 2+ years
- **Follow which population?**
 - All volunteers?
 - Baseline Ad5 > 18?
 - Men only? [vast majority of infected subjects are men]
 - Men baseline Ad5 > 18?



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How Much More Can Be Learned About the Relative Risk (RR)?



*Projections of numbers of infections assume the observed HIV incidence to date continues in the future with no decrease



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What Questions Can Be Addressed?

- Does the trend to more infections among vaccinees reflect a true increase in risk?
 - By pooling already observed events with new events, obtain more precise assessment of **RR**
- If there is increased risk, how long does it persist?
 - Most of the observed infections to date (65 of 82) occurred within the first year after first vaccination
 - The longer-term follow-up will provide assessment of the **RR** beyond one year after first vaccination, based mostly on new infections



Other Discussion Questions on Follow-Up Design

- Frequency of study visits?
 - E.g., every 3 months?
- Duration of additional follow-up?
 - E.g., 2-2.5 additional years?
- Follow for a certain calendar duration or until X events?
- Blinding
 - Neither study participants nor study staff know whether participants received vaccine or placebo. Should this blinding be continued in follow-up?
 - If so, in everyone? In a subgroup?
 - Maintain blind in HIV infected volunteers?



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Interpretation of the Comparison of Infection Rates (the Relative Risk, RR)

- Interpretation of RR influenced by 3 main mechanisms:
 1. Biological effect of vaccine on acquisition
 2. Confounding variables (e.g., differential HIV exposure)
 3. Chance
- **Goal:** Assess the biological effect of vaccine
- With 100% blinding (+ randomization) we expect no confounding, so that the estimated **RR** measures the biological effect of interest



Blinded vs Unblinded Follow-Up

- If all participants are unblinded then the comparison of infection rates measures an **inseparable mixture** of
 - *Biological effect* of vaccine
 - *Behavioral effect* of knowing vaccination status
- The more unblinding, the more opportunity for confounding biological and behavioral effects



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With Unblinded Follow-up, Can We Correct for Confounding?

- Theoretically, statistical models can be used to correct for confounding, by adjusting for group differences in HIV exposure over time
 - However this modeling may fail in practice leading to questionable interpretation of results
 - HIV exposure is measured imperfectly by self-reported risk behavior- can cause the methods to give misleading results
 - Could accidentally conclude a harmful vaccine is safe, or a safe vaccine is harmful
 - The more similar the risk behavior in the two groups, the less reliance on modeling and the more credible the results



Other Aspects of Unblinding that Need Discussion and Debate

- Participant safety and well-being
 - Will risk reduction counseling be more effective if it includes information on treatment assignment?
- Unblinding would allow participants that received a placebo to enroll in other vaccine trials
 - Participants should be able to determine how they will proceed
 - It is important that all participants understand that their greatest contribution to the HIV vaccine field is likely to be remaining in follow-up in STEP, to learn the effects of this vaccine over time
 - Placebo recipients should understand that their follow-up is as important as vaccine recipients. Without the placebo group, we will be unable to interpret results in the vaccine group.



Summary

- The first priority for the STEP study is to protect the well-being of all study volunteers. This will be done through ongoing clinical monitoring, risk reduction counseling, and linkage to prevention and care.
- Proposal for an independent DSMB to follow-up all volunteers at frequent intervals
 - Monitor retention
 - Monitor acquisition rates in blinded and unblinded participants
 - Develop a plan for futility to meet scientific objectives
 - Futility would mean continued blinding of volunteers not useful



Summary

- As part of our commitment to study volunteers and the entire HIV vaccine field, we want to understand the long-term effects of this vaccine
- The discussion that follows will address the best way to assess the longer-term effects of the vaccine, while protecting the well-being of study volunteers



Summary

- If a high percentage of STEP participants will volunteer to remain blinded then it is scientifically compelling to continue the blind
 - Comparison of infection rates (vaccine vs placebo) in those who remain blinded clearly interpretable as biological effect of vaccine
 - Some opportunity to combine data from voluntary blinded and unblinded groups to assess the biological effect of vaccine with greater precision, through advanced statistical methods
- Questions to address:
 - How well can the rate of voluntary blinding be predicted?
 - How to best communicate with study participants to help ensure ongoing study retention and an appreciation of the value of maintaining voluntary blinding?



How Much Voluntary Blinding is Enough?

- Of interest to observe enough infections in the voluntary blinded subgroup to evaluate the RR in that group
- **Example:** Follow-up through March 2010. Projected infections combining already observed and future infections*
 - 197 All men
 - 102 Ad5 > 18 men

Power to Detect a Doubling of the Risk of HIV Infection ($RR \geq 2$) [2-sided .05]

Population	Percentage Blinded						
	40%	50%	60%	70%	80%	90%	100%
All men	84	92	94	98	99	99	> 99
Ad5 > 18 men	49	68	73	76	84	90	91

*Projections of numbers of infections assume the observed HIV incidence to date continues in the future with no decrease



Conclusion

- Longer-term follow-up of HIV uninfected participants is important
 - Follow-up for an additional 2+ years anticipated to more than double the information for evaluating the biological effect of vaccine
 - Will provide further insight into the biological effect of the STEP vaccine
 - Will provide valuable information to guide future HIV vaccine research
- Need further discussion and evaluation of the pros/cons and feasibility of maintaining a voluntary blind