

Investigators' Discussion

1) WSM Abstracts and papers to be discussed

2) Manuscript team to be formed

3) Demonstration Projects

- PEPFAR
- Other

4) Planning for MWANZA results

Messages regarding Mwanza: Prepare to discuss how the studies are similar in dosing, eligibility criteria, and basic concept. Differences: Populations, and frequency and duration of follow-up.

Positive – 1) From a proof of concept perspective- demonstrates that HSV-2 does increase HIV susceptibility...not just a confounder

2) That risk can be modulated by suppressing HSV-2

3) Provides an intervention that can compliment ABC, counseling and treatment of other STIs

4) Reinforce that multiple past studies have suggested as many as 1 of 2 HIV neg African (more in some subgroups) women, 1 in 4 Americans, 1 in 3 South Americans infected for life

4.5) One or two in 10 people with genital herpes has symptoms that they recognize

5) Safe- has been used for up to 10 years

6) Envision that targeting HSV-2 is a powerful intermediate before microbicides or vaccines

7) Can be implemented immediately- generic, very safe, well studied, minimal side effects, no monitoring needed

8) If asked about resistance, note that previous trials have shown no increase in resistance

9) Be prepared to get critical information across in a 30 second sound bite- provide more detail after, if sought

10) Reassure people that there is a follow-up study coming out to validate

11) Be prepared for scale-up questions

A) cost

B) current use

C) Availability

D) Engaging other partners, such as PEPFAR, Clinton Foundation to address drug availability and cost

E) Country approval of roll-out

F) Prioritizing who gets it and duration: further research needed- honestly, our data don't say that- one of the many important questions to be worked out with careful review of current and future data, in consultation with WHO

G) Can participants maintain this regimen?

H) Diagnostics- cost, availability, specificity and sensitivity in these populations

- 12) Recognize that most countries will await guidance for WHO, and we are actively involved in those discussions
- 13) Modeling for cost effectiveness analysis- which groups most beneficial
- 14) These results show the need to develop an HSV-2 vaccine

NOTE: Respond to questions directly, honestly. If you don't have an answer, show that you've considered the issue and are aware of the next steps needed.

Indeterminate or No Significant Effect

Various scenarios:

Underpowering: lower adherence, lower effect, lower incidence, drug sharing (intentional or accidental), under-dosing (especially in context of tighter shedding windows) or better product choice- valacyclovir? But HPTN 039 may be able to power it. Might be able to tease out reasons by comparing two studies. Mwanza will need to do a per-protocol analysis. In this case would need to find more money somewhere to do more urinalysis to see about drug sharing.

Harm

People got herpes suppression, but with lesser symptoms or by thinking they were protected by taking any pill, were then disinhibited from performing riskier sex

Place in context of the general epidemic- that even those who were at higher risk in the trial were more protected than people in the general population (clinical trials are not putting participants at greater risk)

Analysis

Analysis plan already extant will include ITT and per-protocol analyses, secondary endpoints and adherence. These will be the primary paper. Interactions with adherence and risk behavior over time.

What are the things within **WSM subset** that are unique- concept papers and analysis plans. Start with 2pg. description of question, subset of data, analysis plan, forwarded to 039 protocol chairs, then Jim Hughes, then further review. Try to get this done in the next few months so that SCHARP will not get it when they are swamped with 039 main study close out activities

Using the screening database- comparing screened to enrolled. Data available: reasons for not-enrolling, HIV status, HSV-2 status, demographics, basic sexual risk/activity, age, site, education level.

Symptom reporting- selecting subgroups for targeting an intervention. How many people report tingling or burning as marker for re-activation? Report on number of recurrences by arm in the main paper. Why are dispensations of open label so low? Sinead- Probably people are not coming in if they have an outbreak between visits. Is there an increase in symptom reporting as a counseling effect over time? How many

women would have met WHO criteria for suppressive therapy if they had known what to report?

Does symptom recognition go up as a counseling effect?

Compare how many people reported symptoms/outbreak in the last 90 days, but didn't come for episodic therapy.

Are the demographics or prior outbreak history able to predict who will be more adherent?

More self-reported symptoms before menses...a real effect? Do we have the menstrual data to do this analysis? Only if it happened to be included on the site-developed medical history form (non Data-fax).

What can be made of the GUD data? Important to point out that our swabs were collected not only from gaping ulcers (classic STD-clinic presentation) but opportunistic collections of minimal signs (e.g. erythemic patch) present at visits.

Is there something to say about pregnancy in the context of HSV-2, and in terms of were the pregnancies planned, or terminated, and (for other trials in future) how was pregnancy managed in our study? What is incidence data for pregnant women? What effect (if any) does ACV have on pregnant women and/or their delivered infants? Should this be a separate paper or part of an incidence paper (probably separate)? Probably appropriate to have parallel papers for Mwanza and 039 data.

Throw everything in one big paper: What is the natural history of symptoms in HIV negative women in Africa?

Another separate paper- what are predictors for seroconversion among HSV-2 infected women in Southern Africa?

Should there be exit counseling for couples? E.g. hey guys, you have an HIV negative woman here.

We can look at the blinded data now and see if we have enough numbers to do these studies prior to unblinding.

5) Post-trial access

6) ACV access survey

7) Media communication plan

(see Elevator Discussion Later in the report)