

Rectal Microbicides Update: Nonclinical Evaluation

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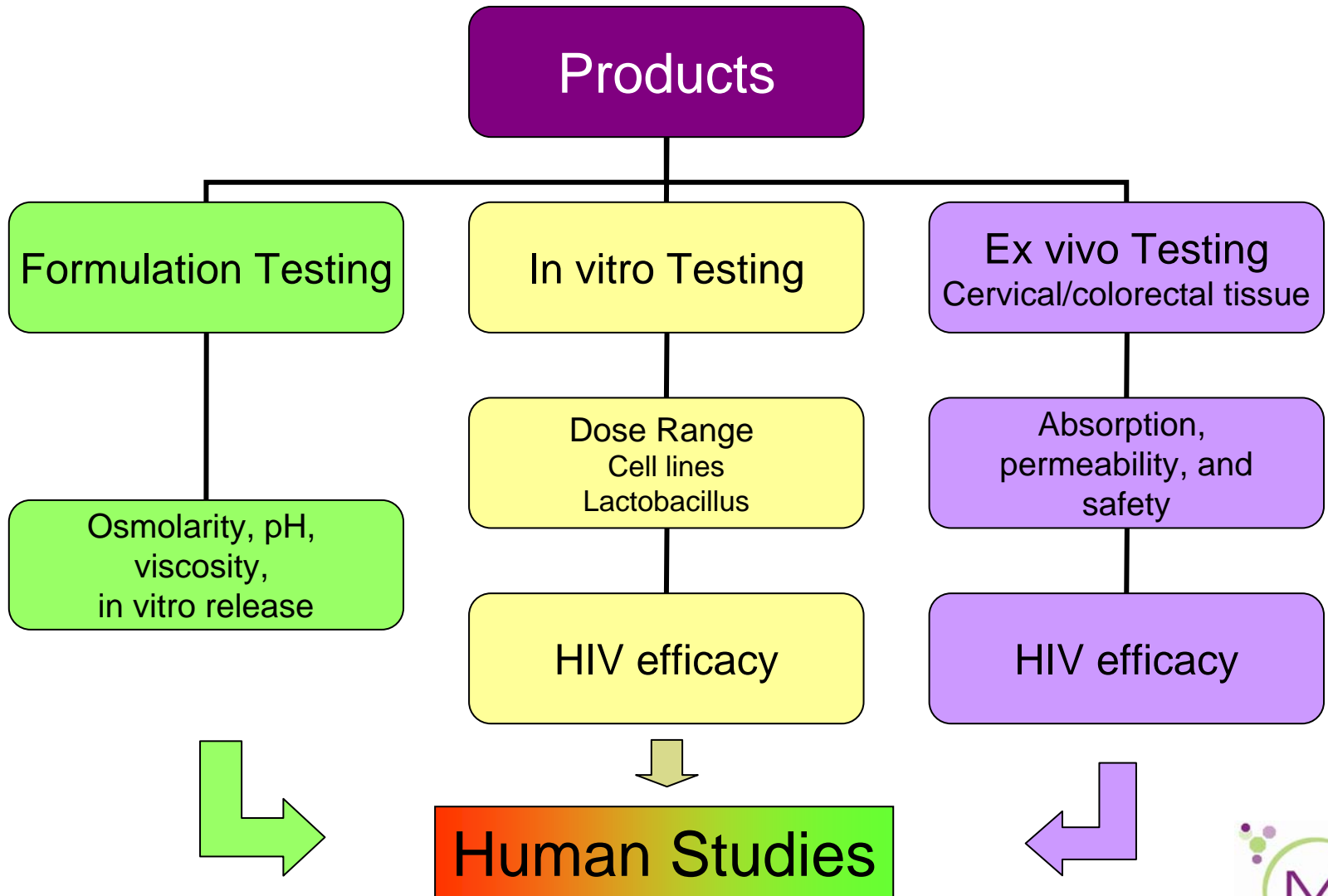
Microbicides 2008 Delhi India Feb. 24, 2008



Nonclinical Evaluation

- Appropriate testing systems.
- Validation of the systems used to predict clinical success.
- Standardization of in vitro/ex vivo testing to allow comparisons between products/formulations.
- Continue to develop new and improved systems for microbicide evaluation.

MTN algorithm



Why do we evaluate microbicides?

- Companies may not have complete anti-viral testing.
- We can comparatively evaluate new products to ones that show promise and others that don't.
- Safety and effectiveness of products are evaluated with an emphasis on explant cultures.

Explant Cultures

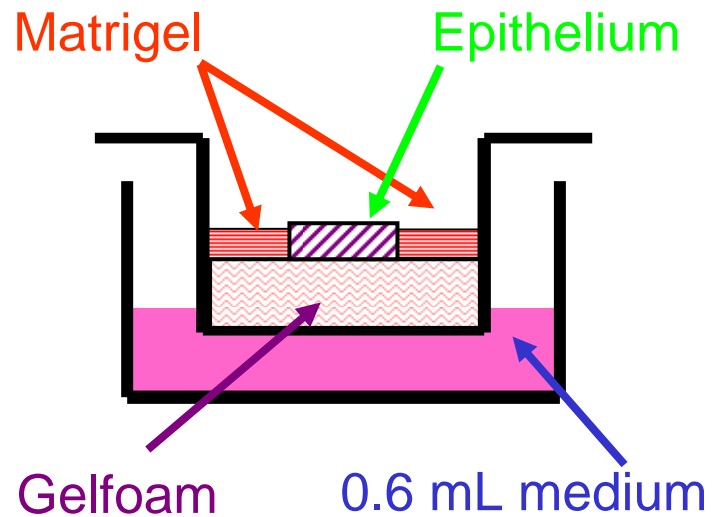
- Cervical and colorectal tissues are where the virus and product meet.
- They have the capacity to quickly and efficiently evaluate multiple product formulations.
- There is the potential to validate the explant cultures to predict clinical outcomes.

Explant Cultures

- **To date, explant cultures offer the best bridge between in vitro testing and in vivo experimentation.**
- We will focus on the colorectal explant culture for this talk.

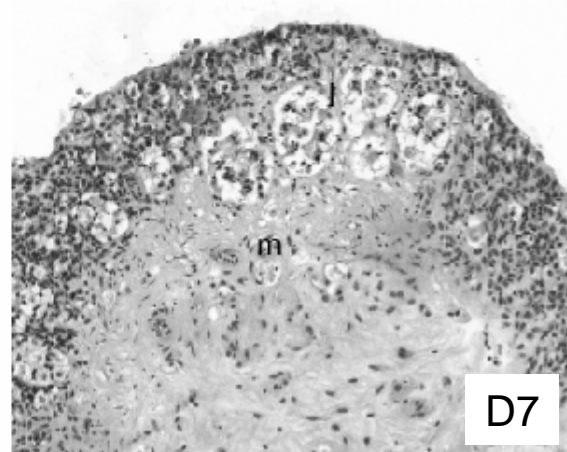
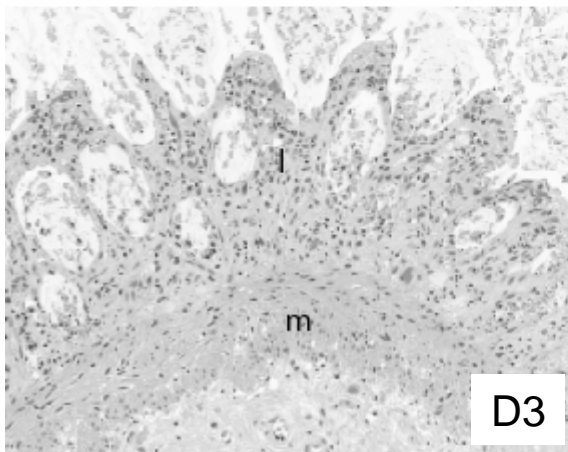
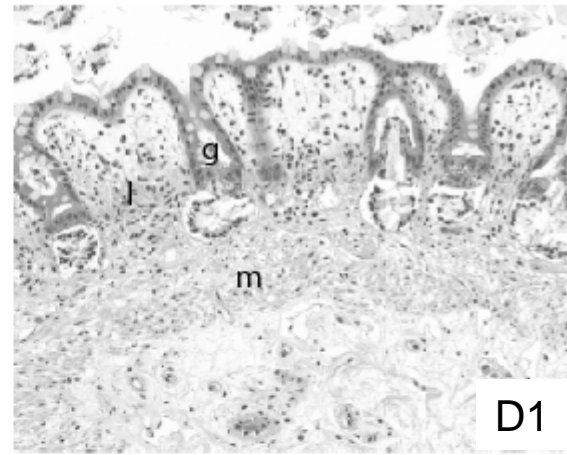
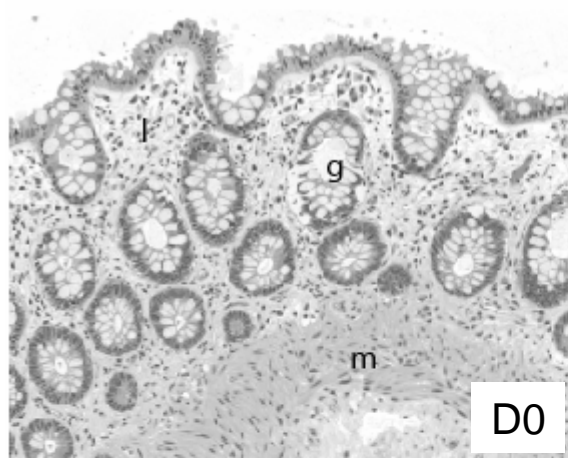
Colorectal Explant Culture

Normal tissue is excised within 2 h of surgery from patients undergoing noninflammatory associated resections



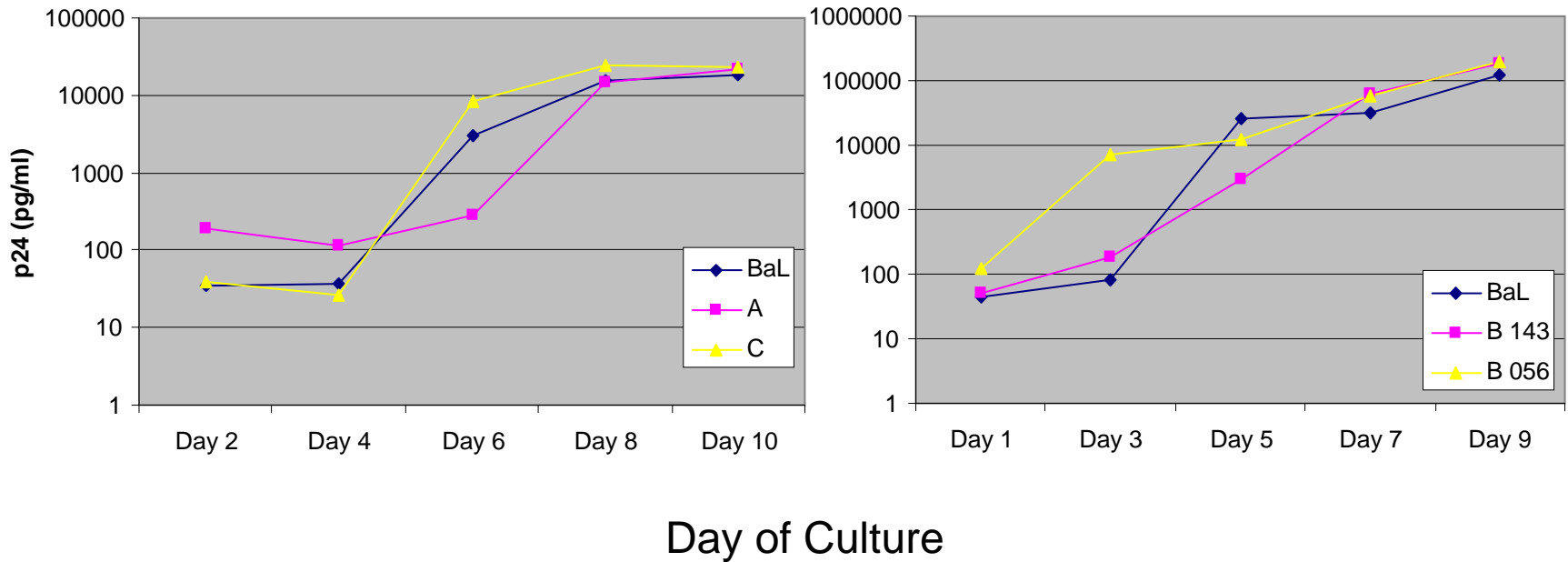
S. Abner et al. **A Human Colorectal Explant Culture to Evaluate Topical Microbicides for the Prevention of HIV Infection.** *J. Infect. Dis.* 192:1545-1556, 2005

Colorectal Tissue Histology



Original magnification 50x

Colorectal Replication of HIV-1

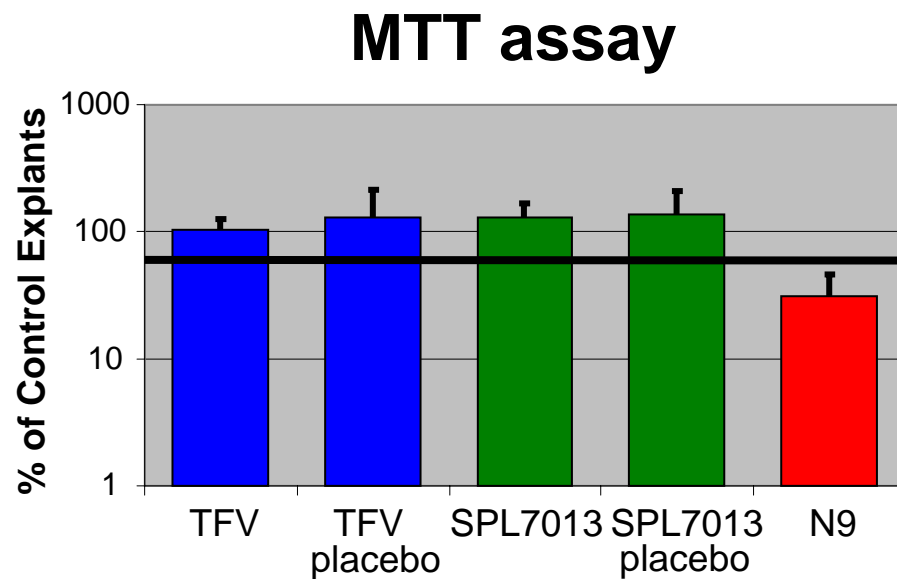


Current Microbicides

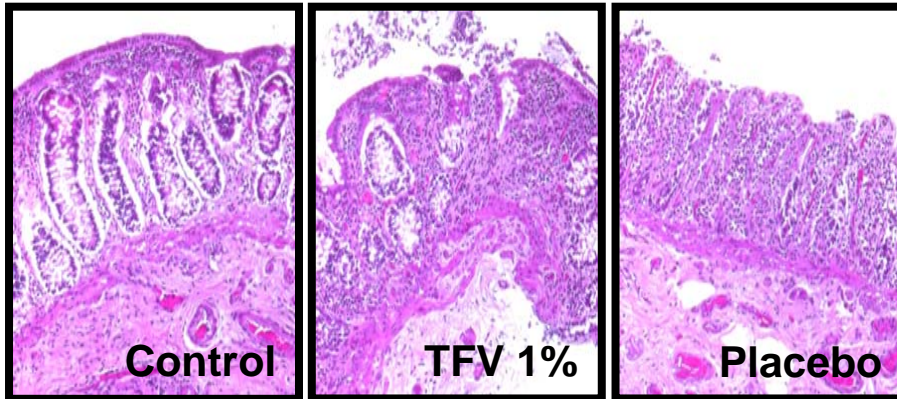
- Tenofovir 1% gel – NRTI antiretroviral (PMPA) formulated into a topical gel.
 - Provided by Gilead Sciences, Inc., Foster City, CA USA.

- Viva gel – Dendrimer, 3% SPL7013, formulated into a topical gel.
 - Provided by Starpharma, LTD, Victoria, Australia.

Product Safety

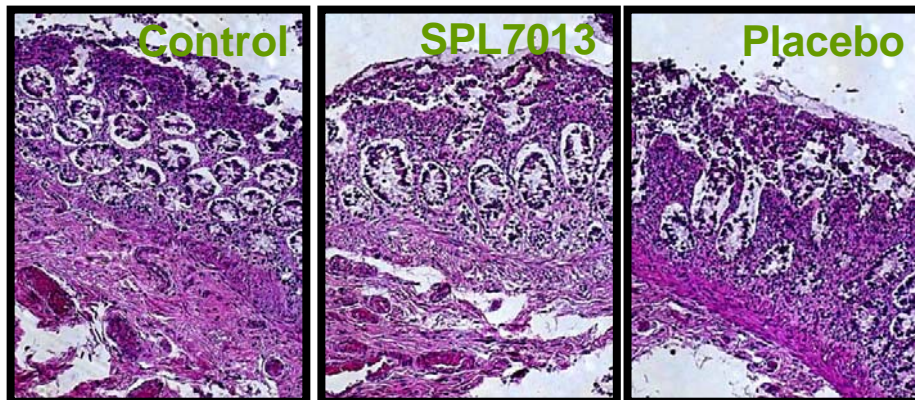


Product Safety



TFV	Active Drug	Placebo
Osmolarity	3347 nmol/kg	3189 nmol/kg
pH	4.45	4.39

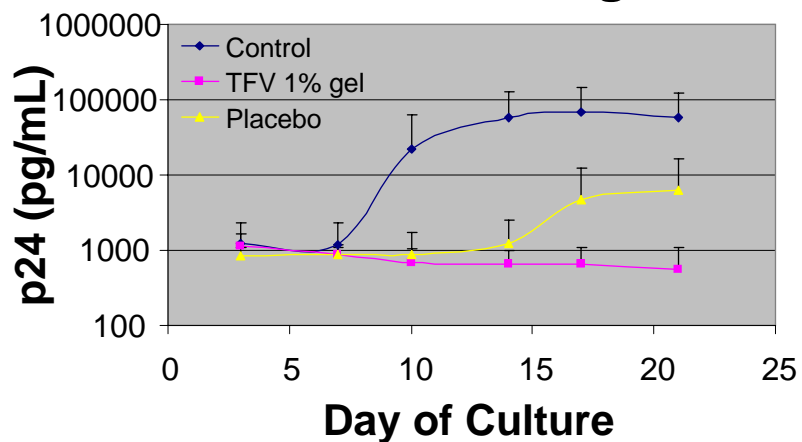
Iso-osmolar is 290 nmol/kg



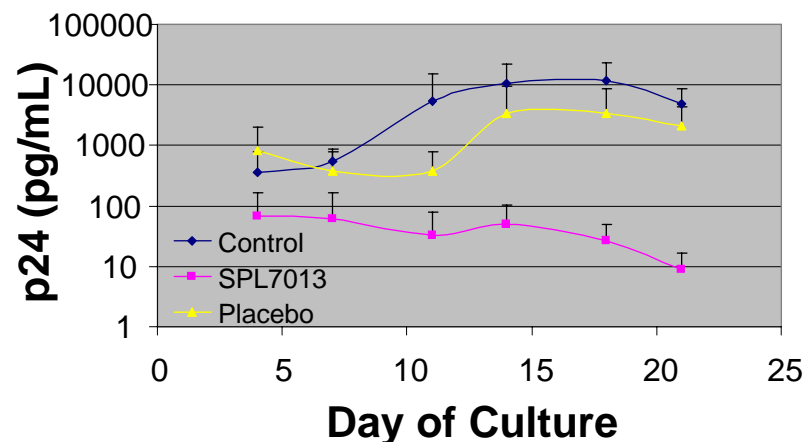
SPL7013	Active Drug	Placebo
Osmolarity	683 nmol/kg	803 nmol/kg
pH	5.25	4.86

Product Effectiveness

Tenofovir 1% gel



Viva Gel



Summary

- Explant models can quickly screen many microbicide products.
- Viva gel was relatively non-toxic to the colorectal tissues.
- Tenofovir 1% gel was hyperosmolar and the colorectal tissue showed signs of epithelial sloughing, but viability was good.

Summary

- Tenofovir 1% gel and Viva gel protected the colorectal explants from HIV-1 infection.
- The outcome was similar when cervical explant cultures were used (data not shown).

Nonclinical Evaluation

- Appropriate testing systems.
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- Standardization of in vitro/ex vivo testing to allow comparisons between products/formulations.
- Continue to develop new and improved systems for microbicide evaluation.

Additional Information - Posters

- **TA-395** – A Standardized Pre-clinical Evaluation of HIV-1 Growth and Microbicide Efficacy in Tissue Explants.
- **TA-215** – Impact of Semen on HIV-1 Infection and in vitro Antiviral Activity of Topical Microbicides.
- **TA-216** – Modeling Topical and Oral Tenofovir Administration Using Cervical and Colorectal Explant Cultures.

Acknowledgements

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Questions

