

Challenges and opportunities in clinical development of antivirals

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Disclosures

- Funding: NIH, Moderna, GSK, Assembly Biosciences
- Consulting: Aicuris, Innovative Molecules, GSK, Heidelberg Therapeutics, Vir

Today

- Historical approach to antiviral drug development
- Validating surrogates for clinical endpoints in herpesvirus infections in drug development

Timeline for development of drugs for HSV

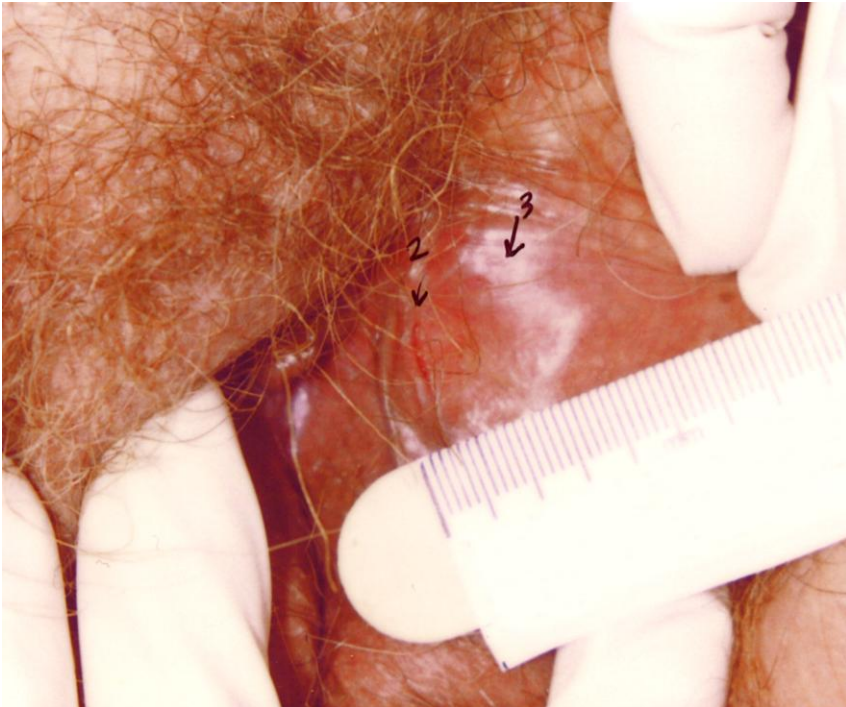
- 1982 – acyclovir approved as topical ointment and IV
- 1985 – oral acyclovir
- 1994 – oral famciclovir
- 1995 – oral valacyclovir
- 1995 – foscarnet for acyclovir-resistant HSV

Drugs for HSV: the olden days...

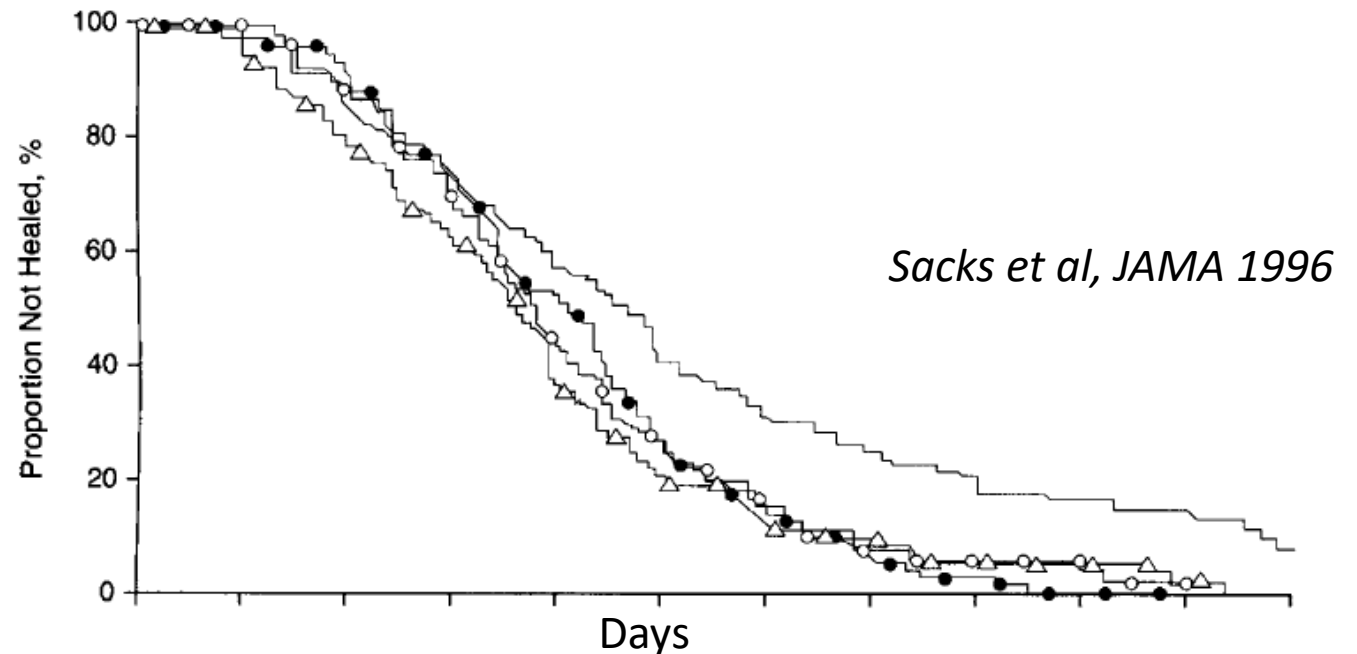
- 1982 – acyclovir approved as topical ointment and IV
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- 1995 – foscarnet for acyclovir-resistant HSV
- Lesion/episode healing for episodic therapy (primary and recurrent genital herpes)
- Proportion of persons without recurrences at 6 or 12 months for suppressive therapy

Endpoints in episodic therapy for HSV

- Clinical assessment of lesion healing not that accurate
- Lesions = virus + immune response

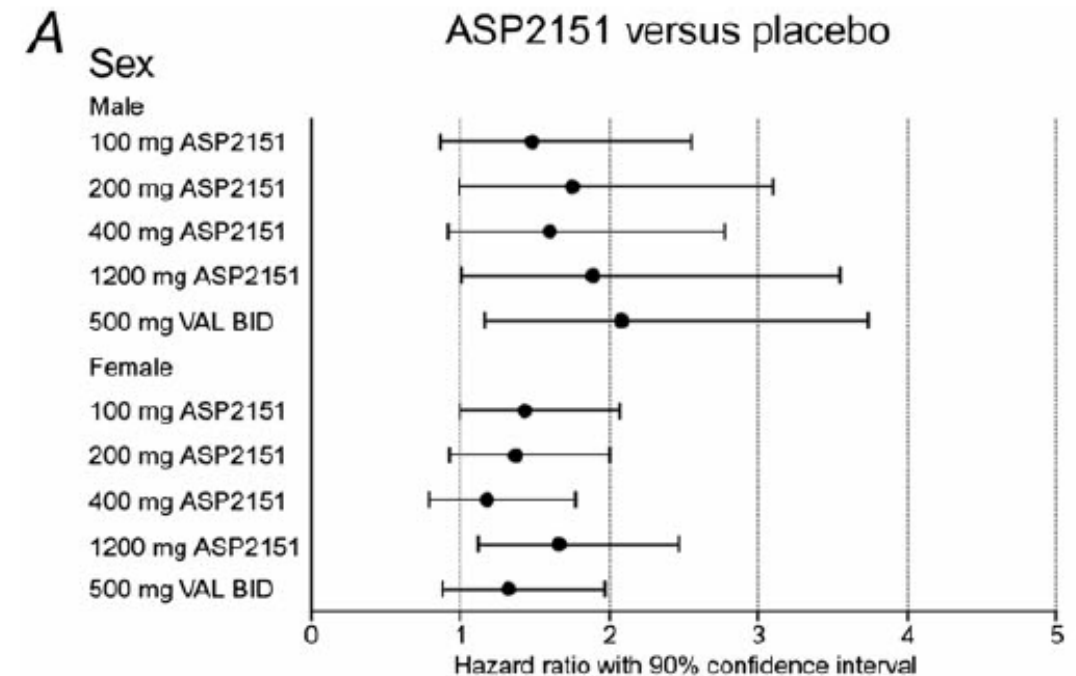


- Famciclovir 125 mg, 250 mg, 500 mg or placebo twice daily
- Drug superior to placebo
- Lowest dose licensed



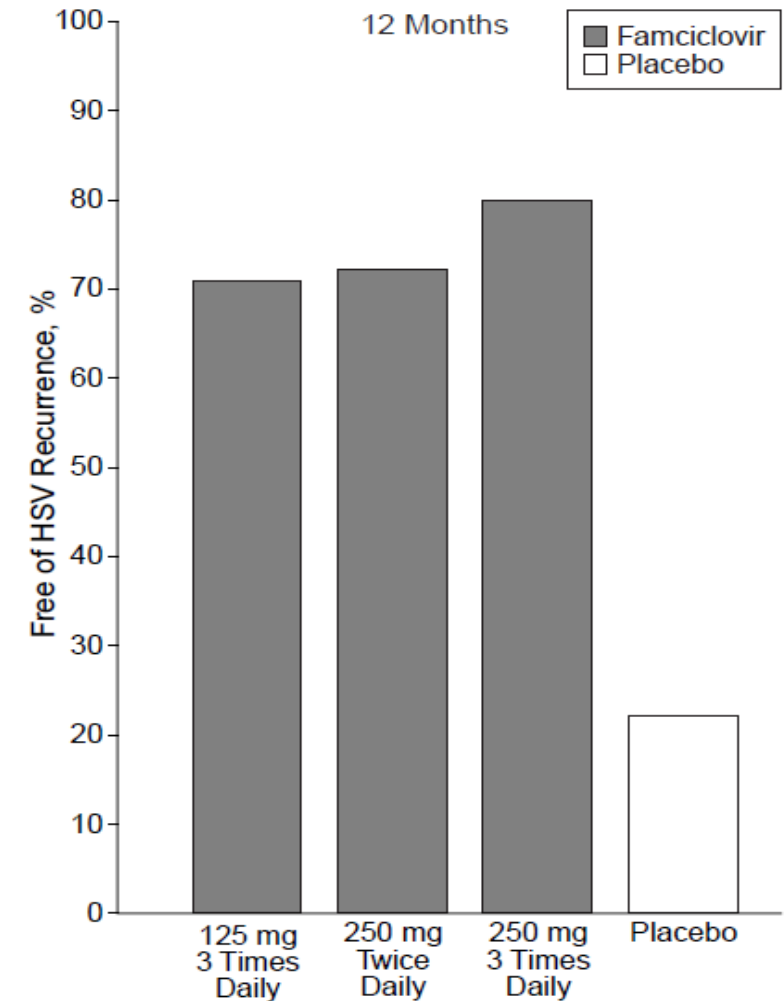
Endpoints in episodic therapy for HSV

- Astellas helicase-primase inhibitor
- Episodic therapy



Endpoints in suppressive therapy for HSV

- Proportion of recurrence-free at 12 months:
 - Patient with 1 recurrence = patient with 8 recurrences
- Not suited well to repeated endpoints (perfect for survival, MI, stroke etc)



Surrogate endpoints: Definitions

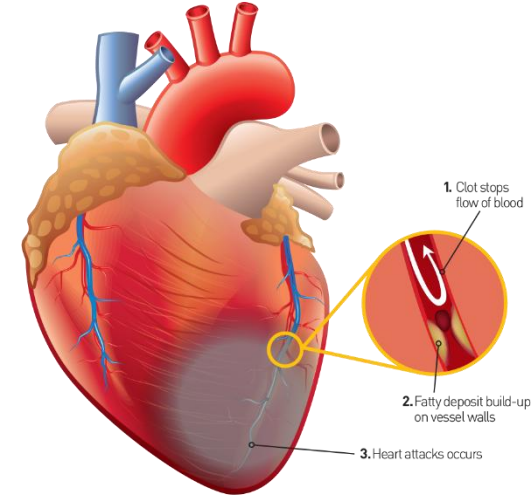
- Clinical endpoint: *a characteristic or variable that reflects how a patient feels, functions, or survives.*
- Surrogate endpoint: *a biomarker or endpoint that is intended to substitute for a clinical endpoint.*
- *A surrogate endpoint is expected to predict clinical benefit (or harm) or lack thereof*

Validating a surrogate endpoint

- A surrogate endpoint is a laboratory measure / physical sign that is intended to be used as a substitute for a clinically meaningful endpoint.
- Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint.
- The surrogate should exist within the therapeutic pathway between the drug and meaningful benefit i.e., the drug results in the therapeutic benefit by virtue of its effect on the surrogate

Validation of surrogate markers

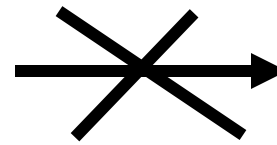
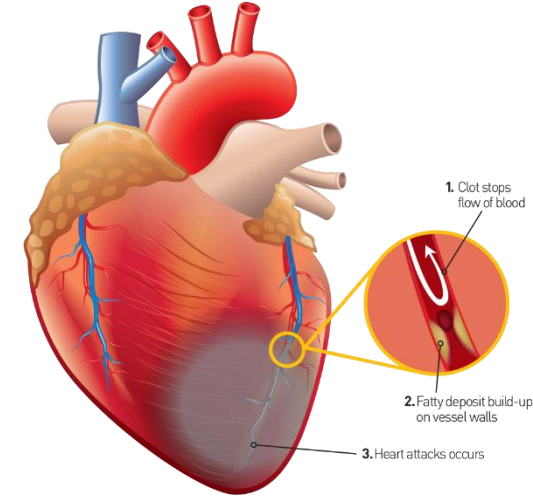
Epidemiological studies:
Hypertension is a risk factor for heart attack



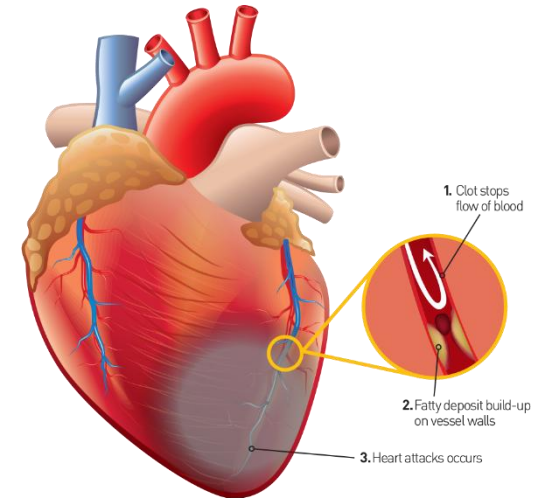
Validation of surrogate markers

Epidemiological studies:

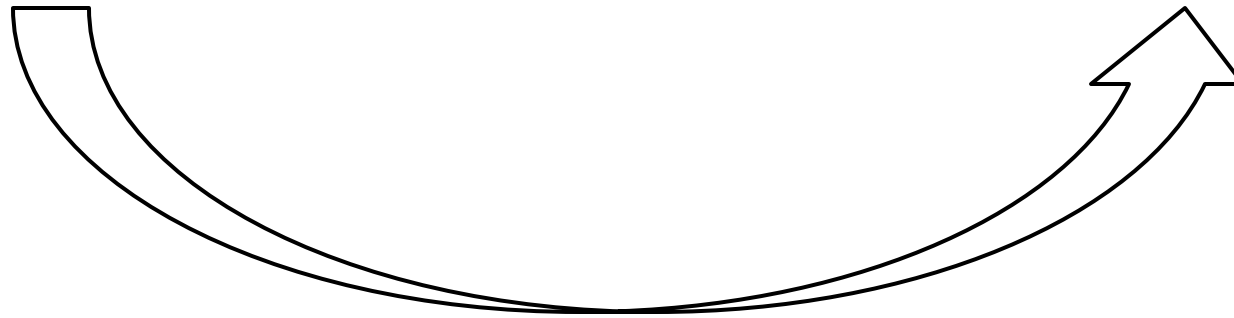
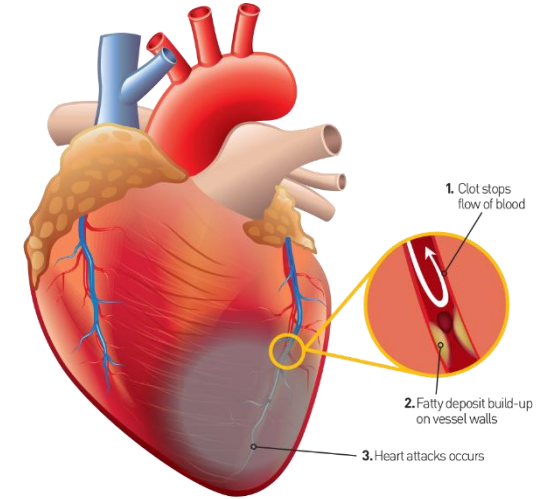
Hypertension is a risk factor for heart attack



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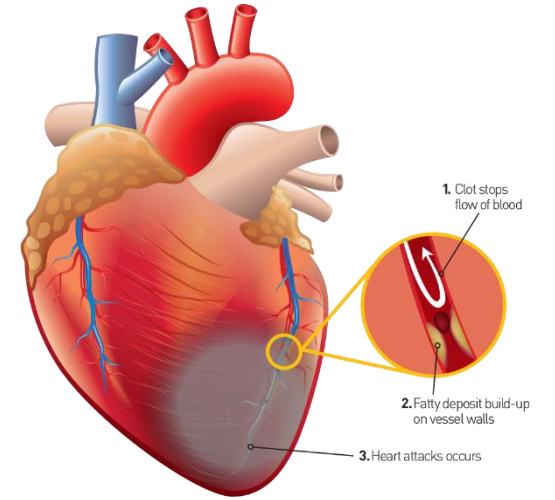
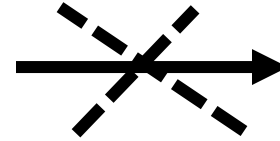


Mechanism of drug action is not always known

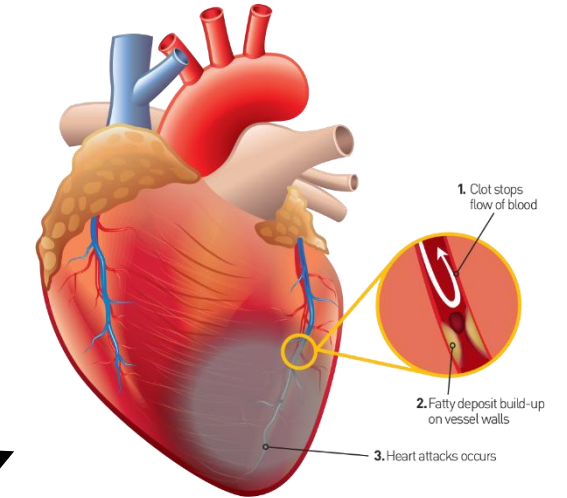
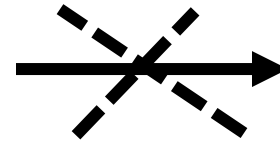


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Validation of surrogate markers

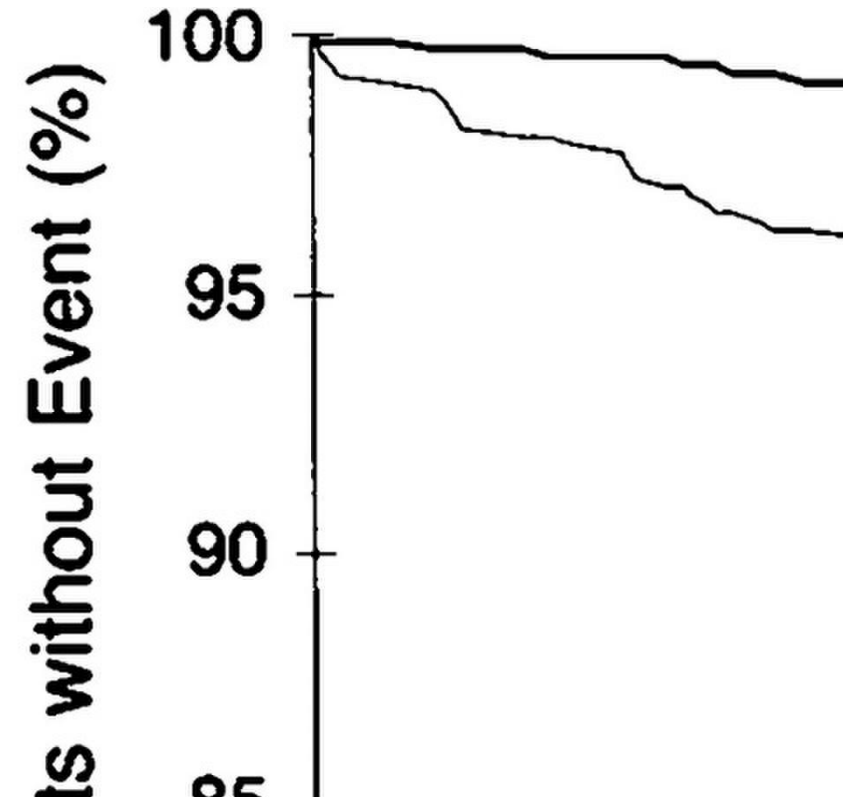


Many clinical syndromes are multifactorial



The Cardiac Arrhythmia Suppression Trial (CAST)

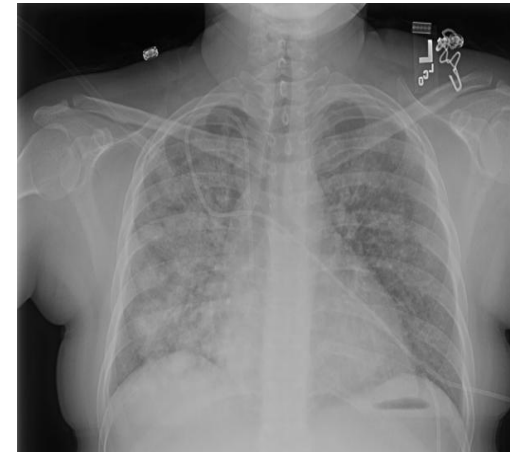
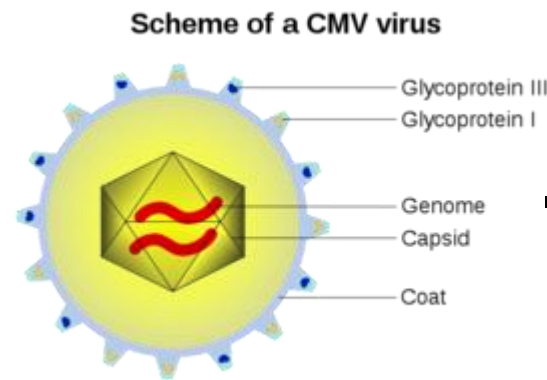
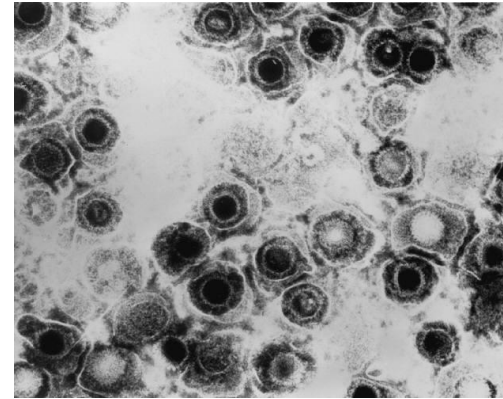
- Arrhythmias lead to cardiac death
- Encainide and flecainide reduce arrhythmias
- Will these drugs reduce deaths from arrhythmias?

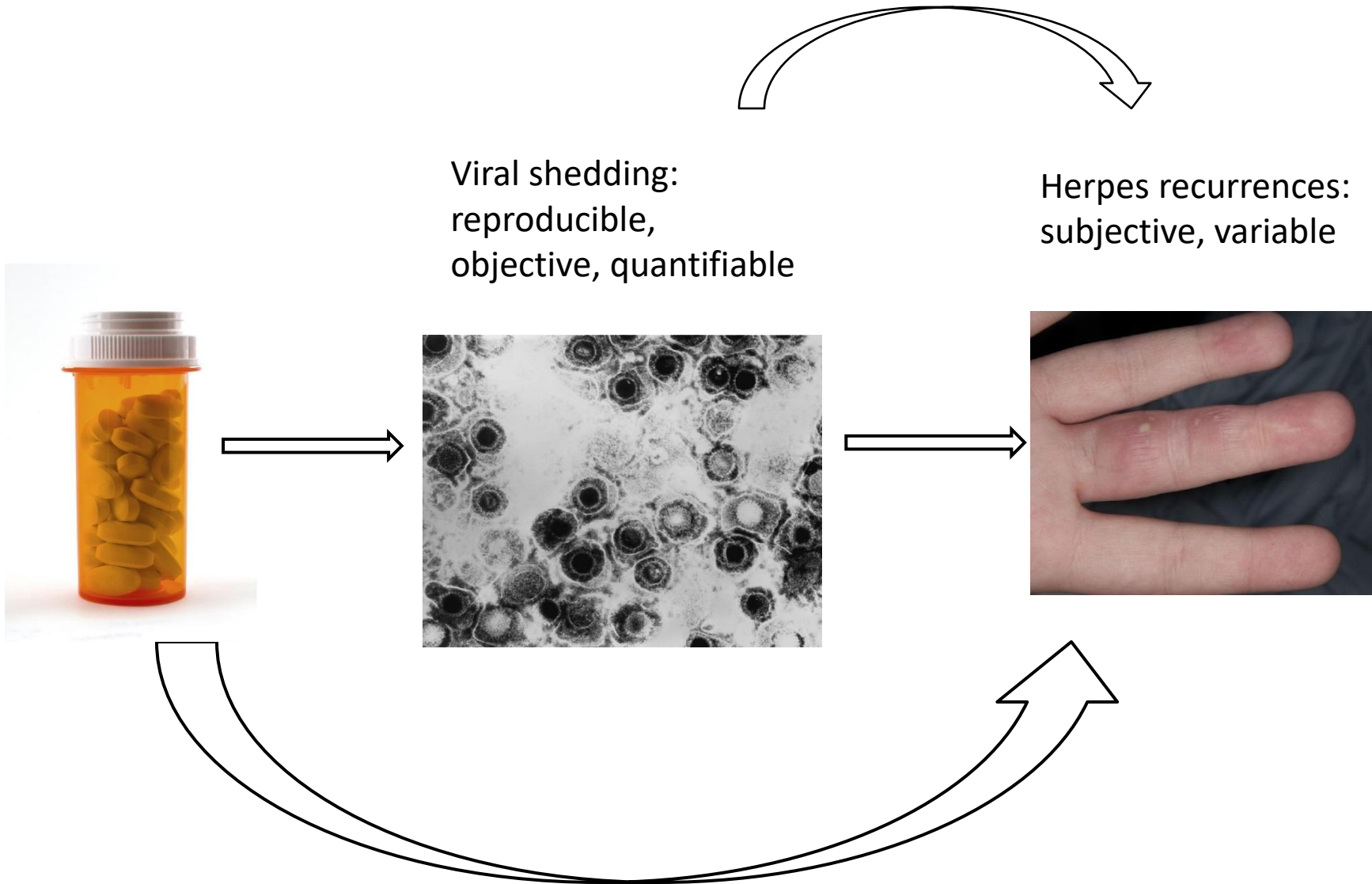


Event = cardiac arrest or death

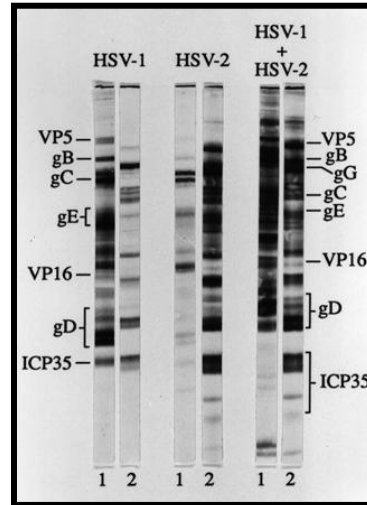
Validating viral shedding as a surrogate marker in development of antiviral interventions

- Unlike chronic disease syndromes, pathogen is required to cause infection-specific syndromes
- HSV infection is *sine qua non* for genital herpes
- CMV infection is *sine qua non* for CMV pneumonia



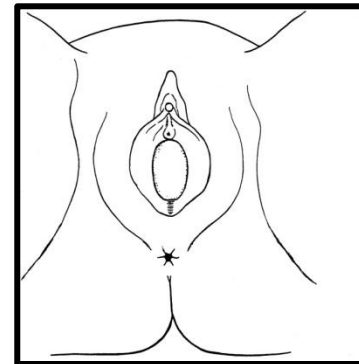


What is the relationship between genital viral shedding and clinical herpes?



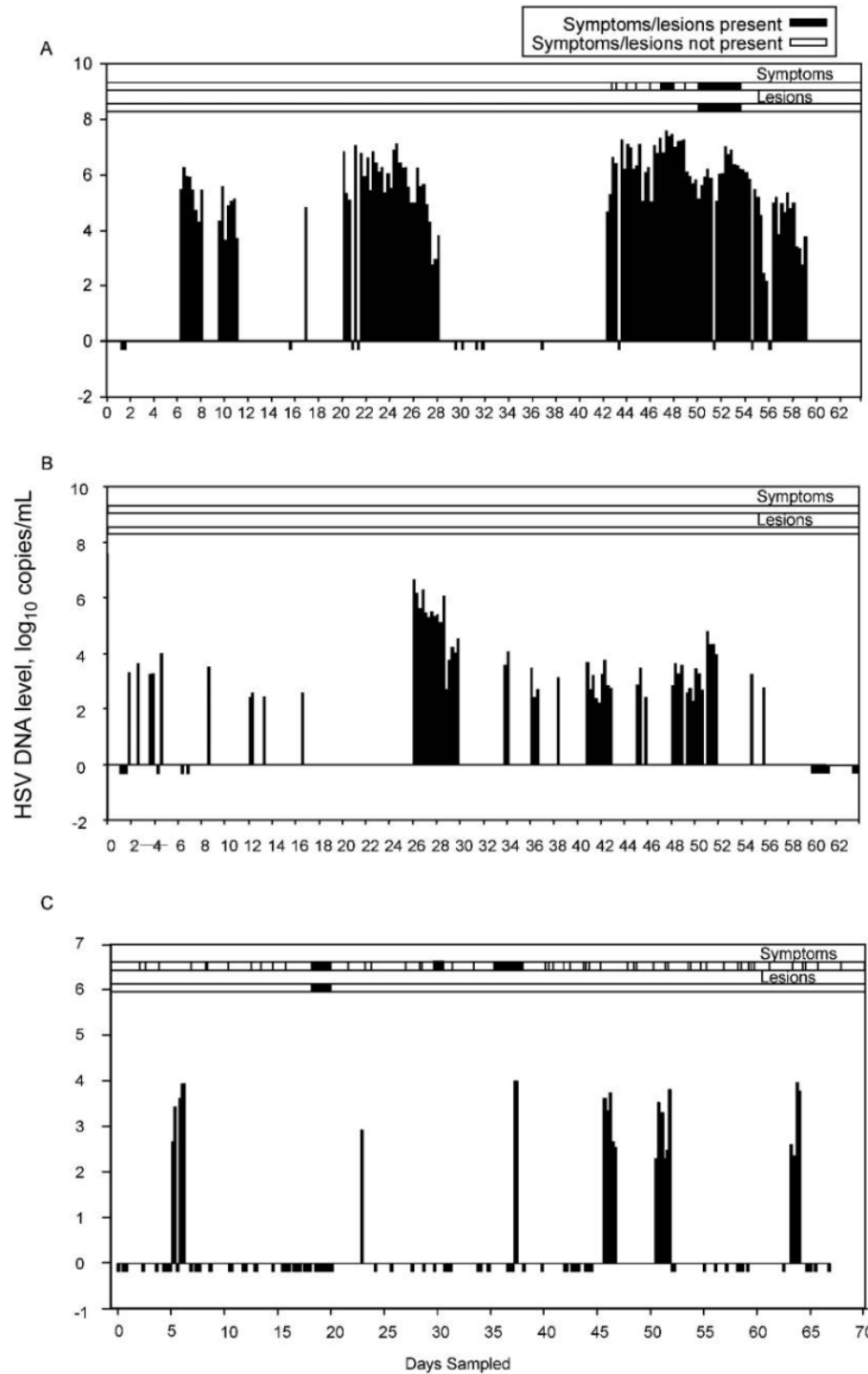
HSV-2 Seropositive Man

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
No symptoms	X	X	X	X	X			X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Itching, burning, tingling													X	X																	
Localized redness or sore spots						G	G																								
Sores, blisters, ulcers, crusts																								G	G						
Abrasions, skin splits, scratches, fissures																															
Thigh or buttock pain or sensitivity																															
Swollen groin or lymph nodes																															
Results of HSV PCR					4	4	4						5	5			4							5	5						



HSV DNA PCR

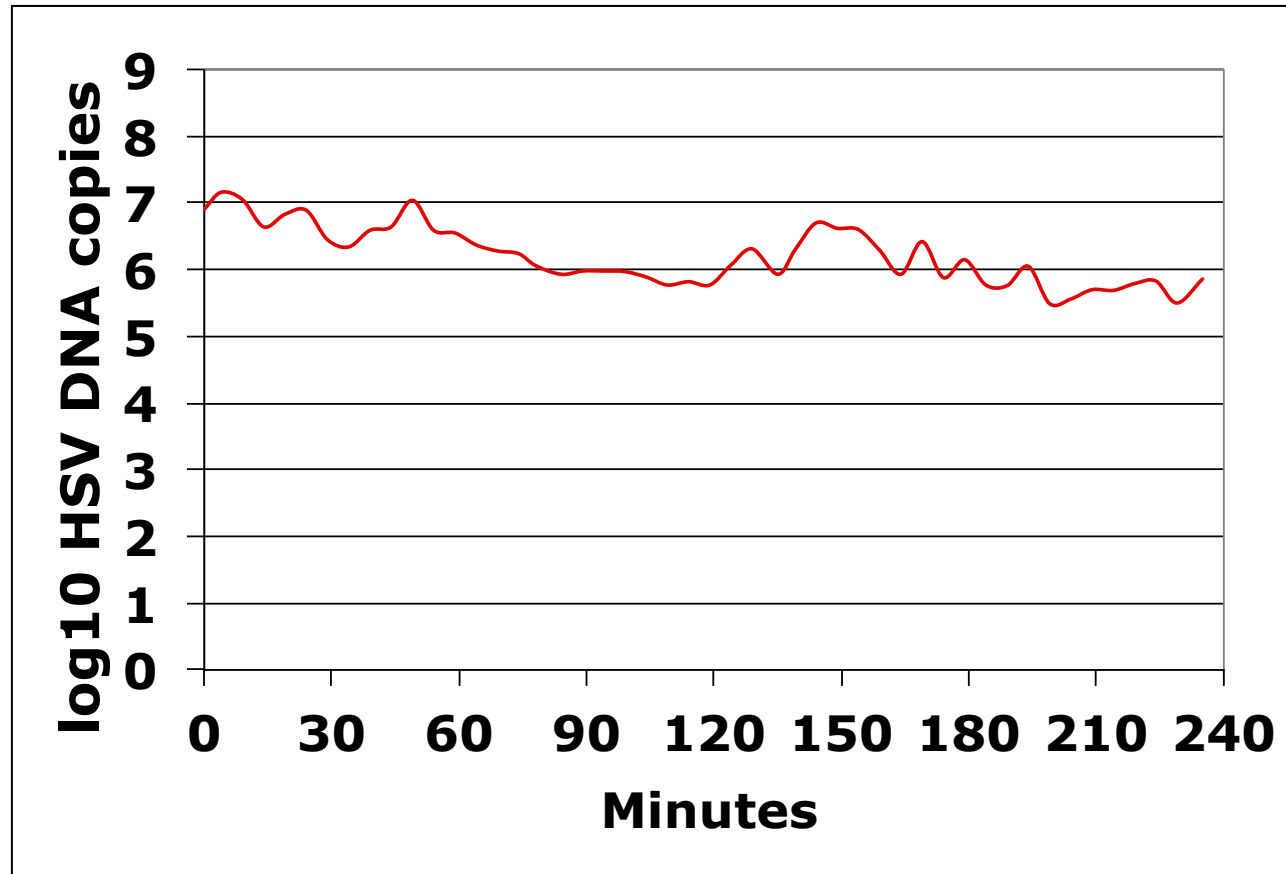
Tronstein et al, JAMA 2011



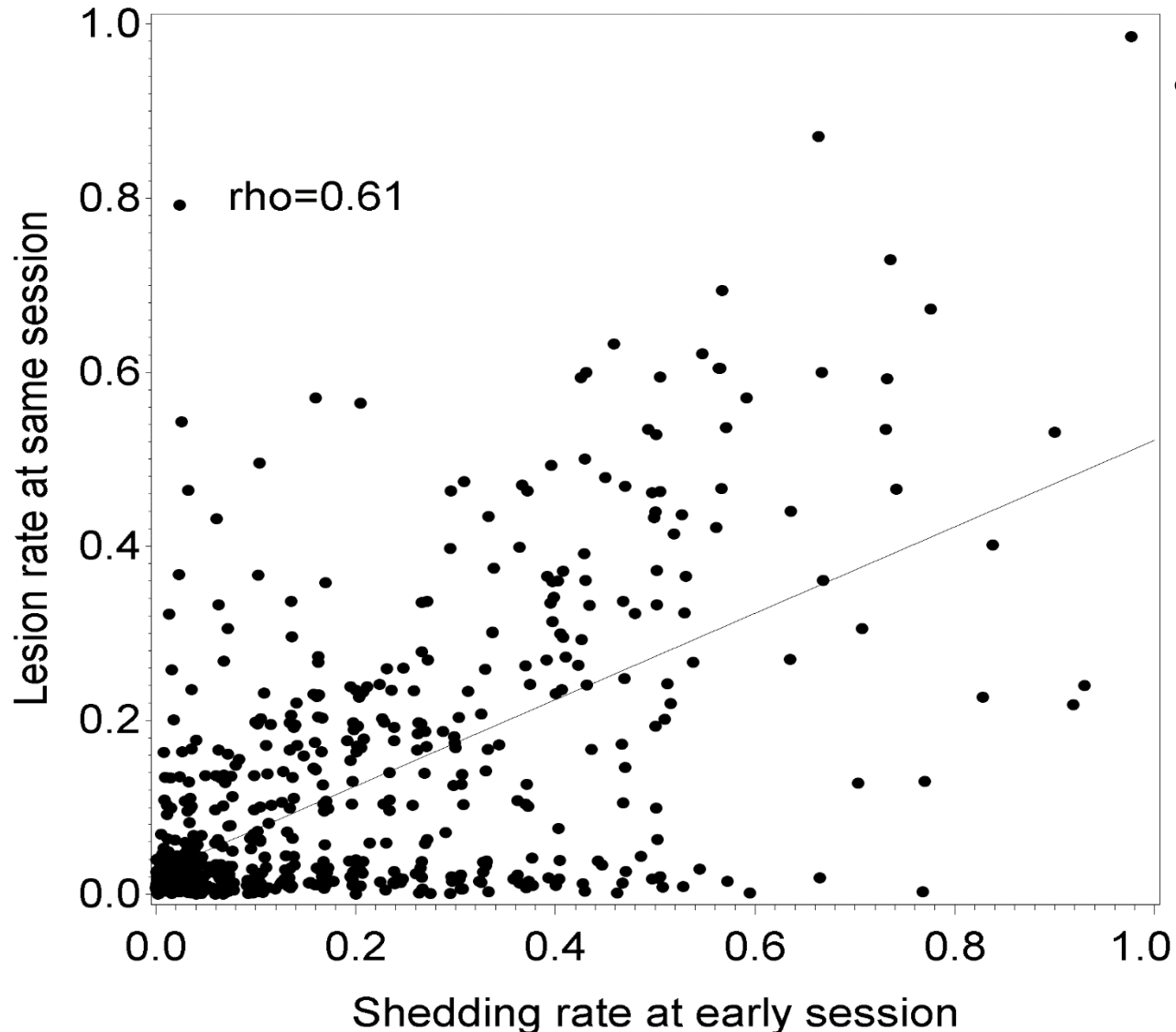
Examples of shedding patterns 4 times/day: variability in frequency and duration

- Variable between people
- Intermittent over time
- More frequent than lesions

Sampling of viral shedding is consistent: q5 minutes swabs

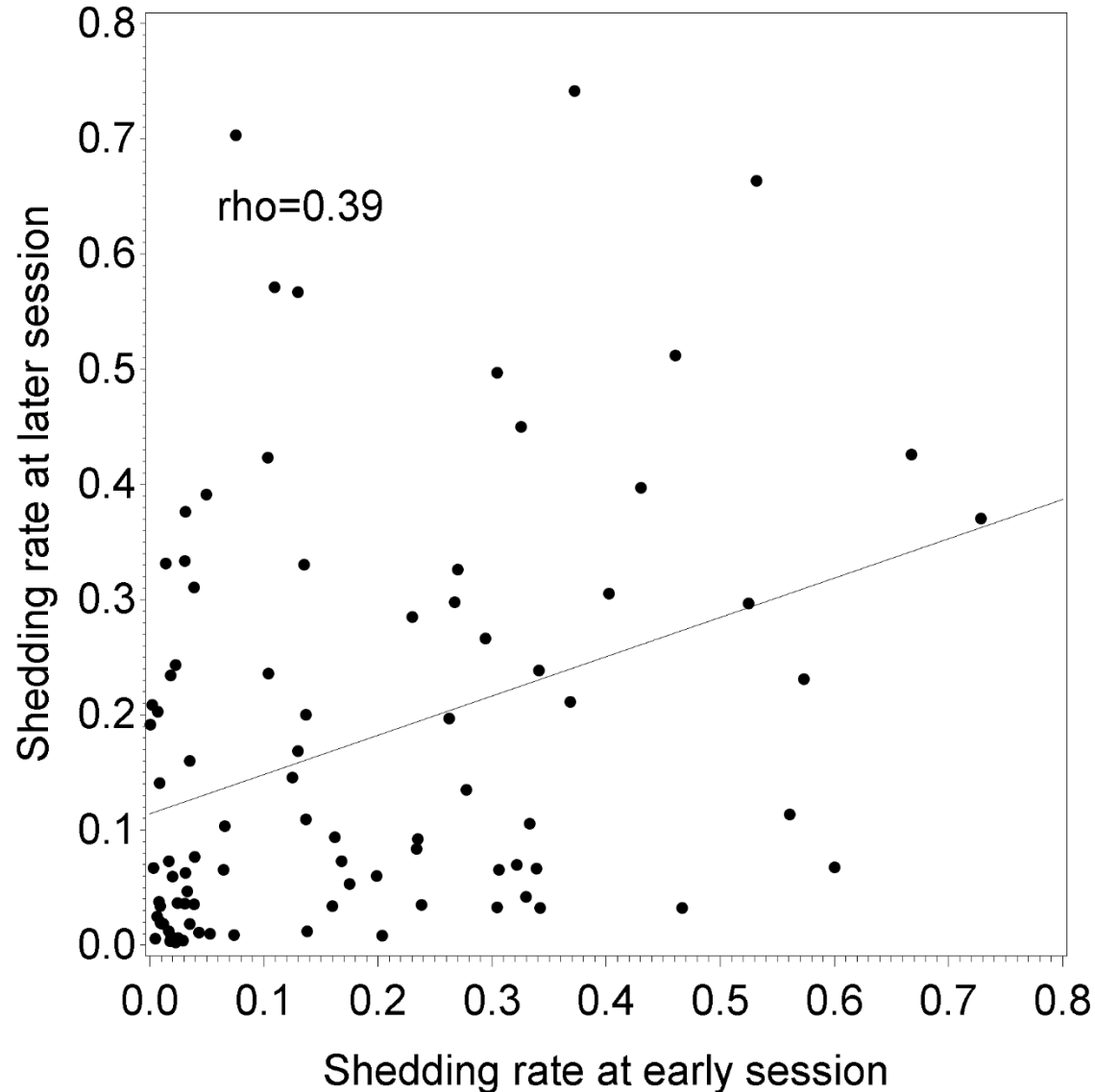


Correlation between viral shedding and lesions



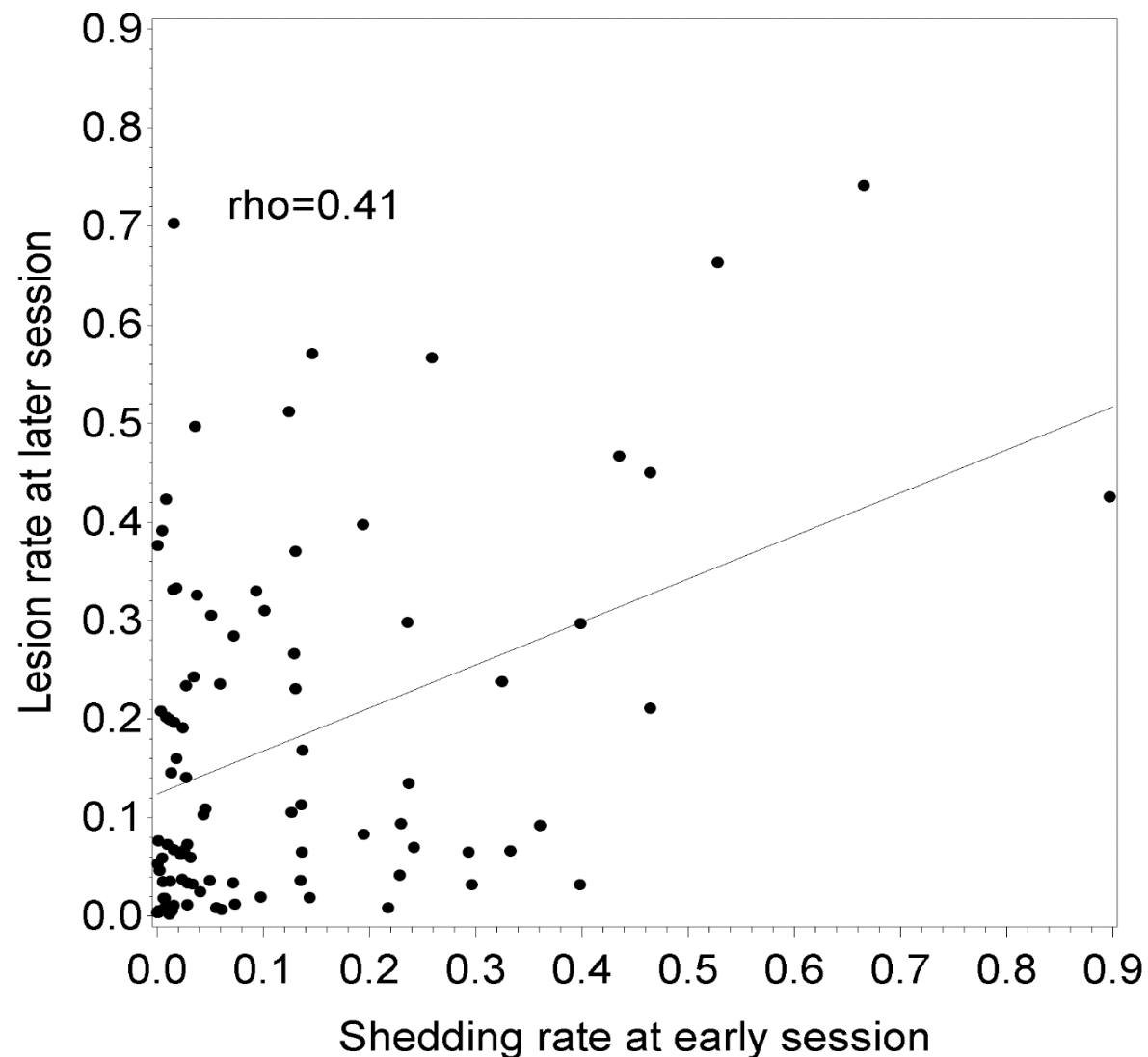
- 674 persons who obtained swabs and maintained a diary for 30 days, $P < 0.0001$

Correlation between 2 shedding sessions



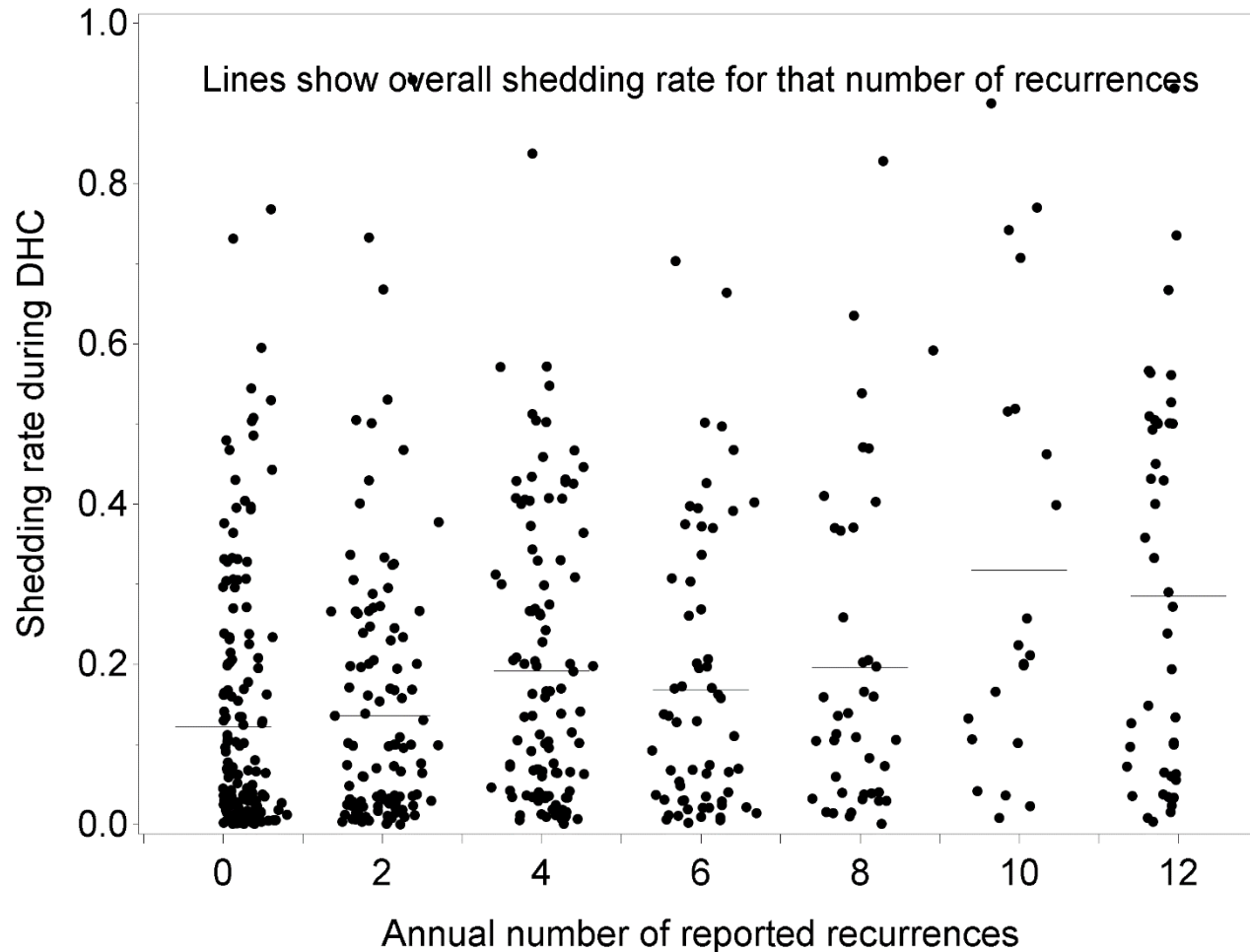
- 90 people, 30 swabs at each time session, $P < 0.001$

Correlation between shedding and subsequent lesion rate



- 90 persons with 2 30-day swabbing sessions, $p < 0.001$

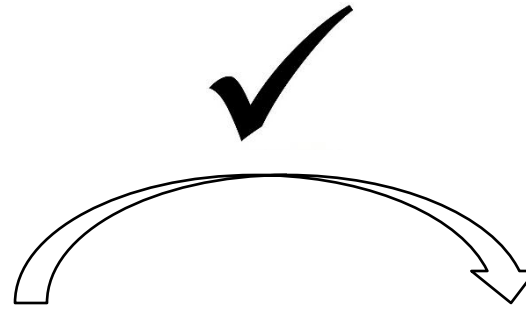
Correlation between shedding frequency and recurrences



- Predicted shedding increases 6% (95% CI 4%-8%, $p < 0.0001$), on a relative scale for each additional recurrence, from 13% for 0 to 26% for 12 recurrences/year

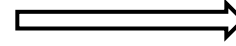
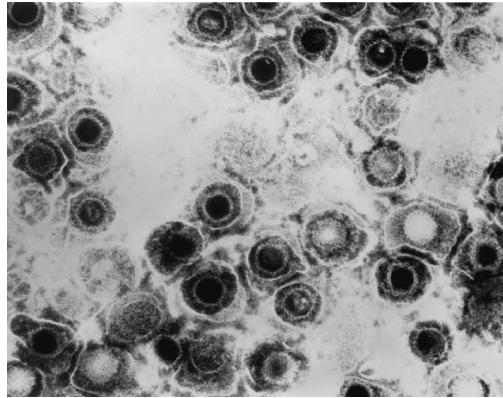
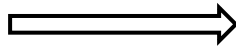
HSV shedding frequency establishes a phenotype for severity of infection

- Consistent over time within individual
- More powerful statistically than lesion rate
- Correlated with lesion rate and recurrence history
- Reported recurrence history in the past year predicts subsequent shedding

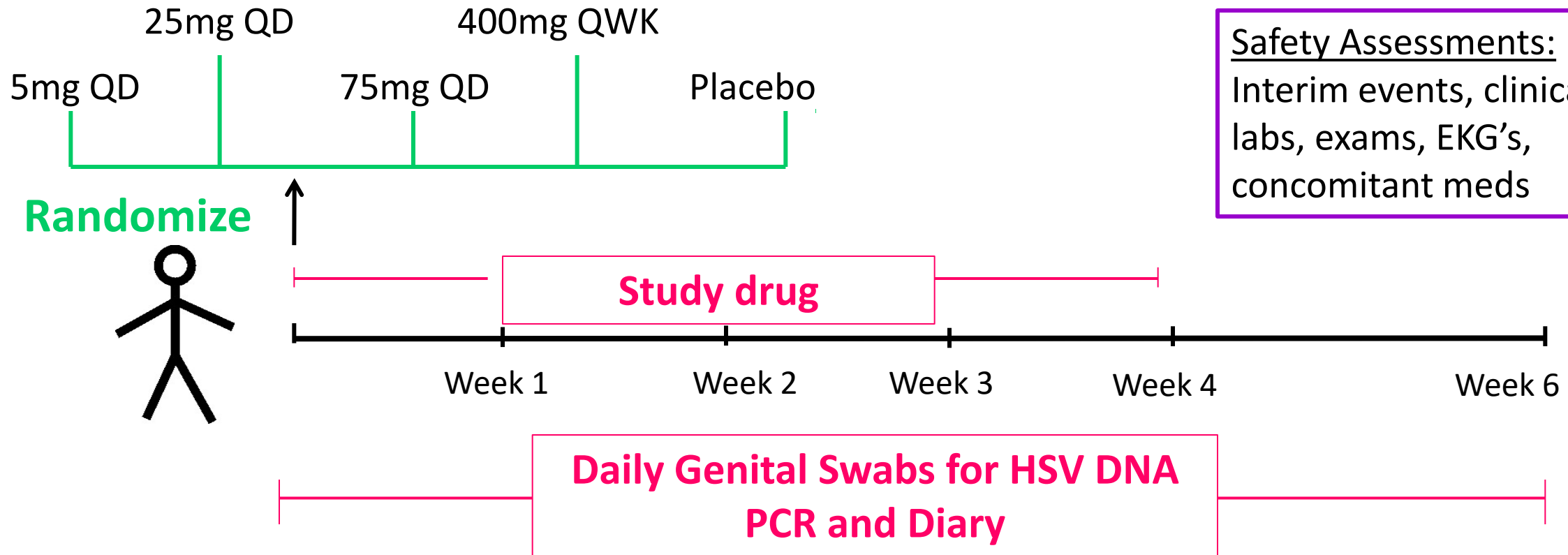


Viral shedding:
reproducible,
objective, quantifiable

Herpes recurrences:
subjective, variable



Study design: dose ranging study of pritelivir



Safety Assessments:
Interim events, clinical labs, exams, EKG's, concomitant meds



AiCuris
Anti-Infective Cures

FEMALE SUBJECT DIARY

Subject Number: -

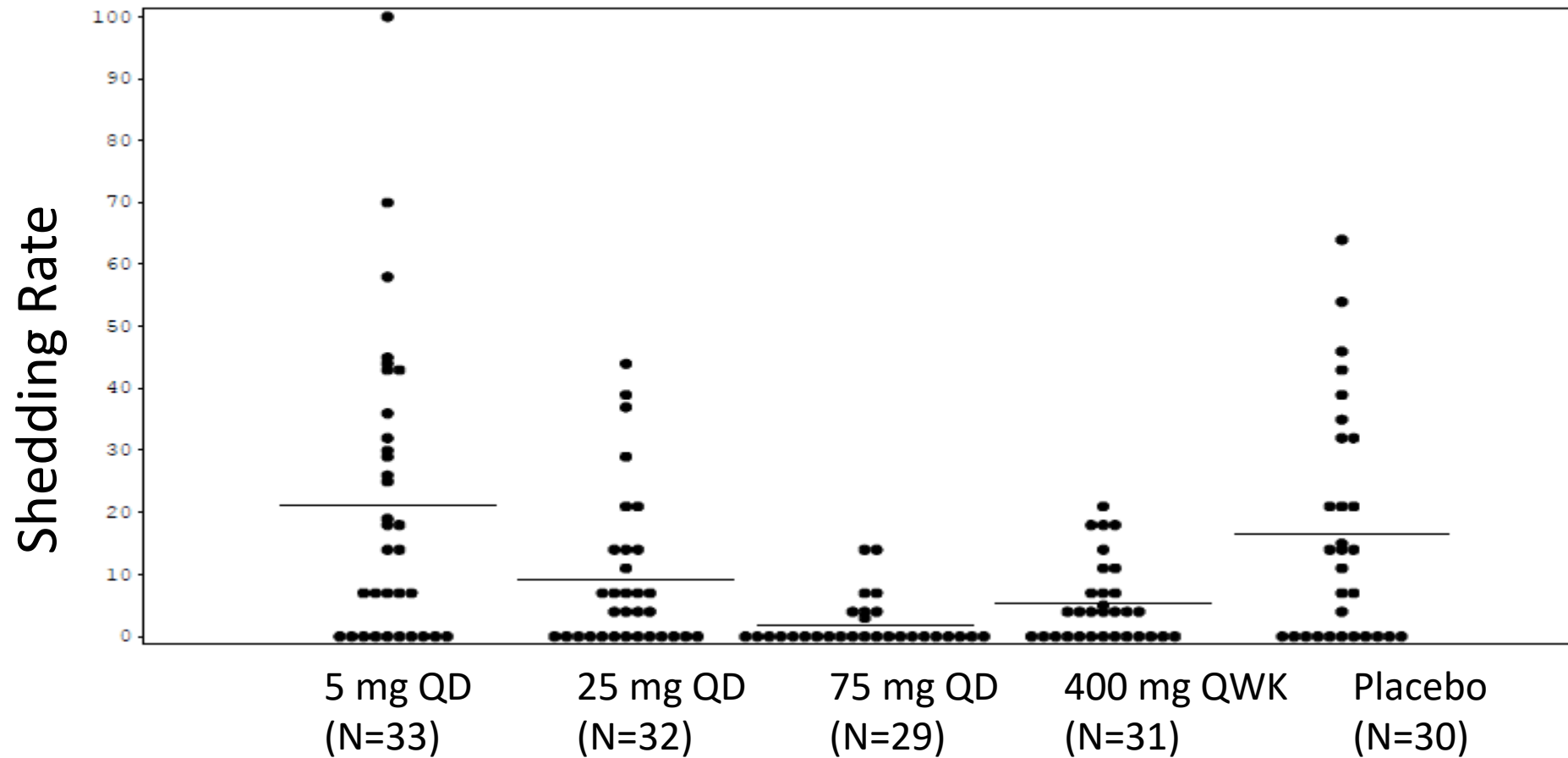
Treatment Period - Day 01 --

Day Month Year

Please print legibly in black or blue ink

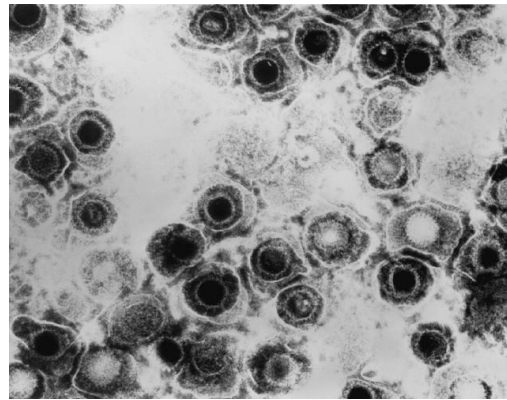
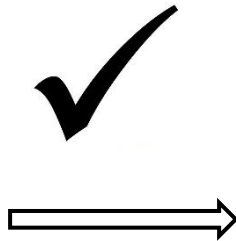
1. Regular daily swab taken? ☐ Yes Time swab taken: : am ☐ pm
☐ No Reason?

Scatterplot of the frequency of genital HSV shedding by pritelivir treatment group: established antiviral effect & identified dose for further development

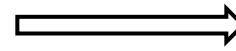


Each point indicates viral shedding rate from a single participant and each line indicates the mean shedding rate for that arm.

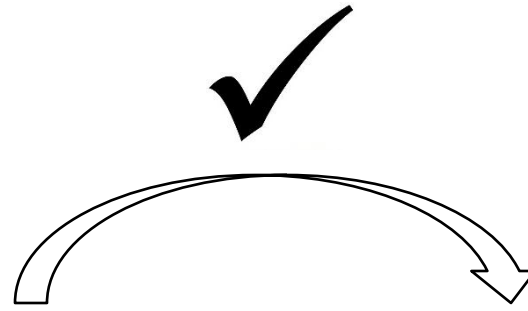
Wald et al, NEJM, 2014



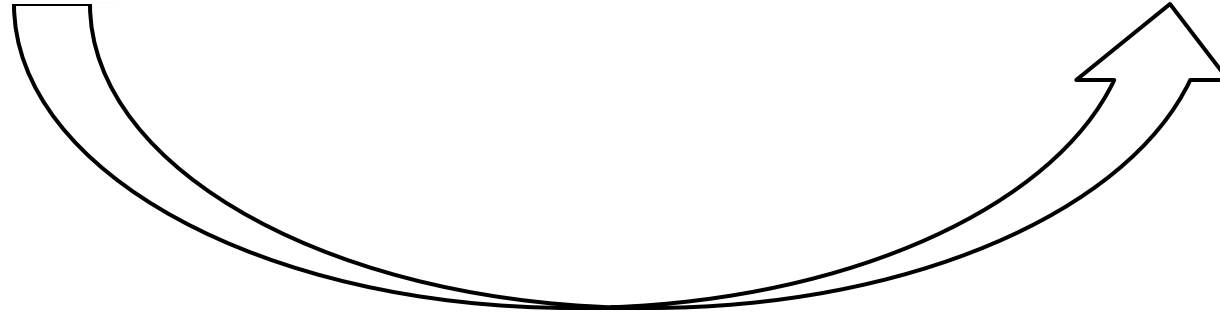
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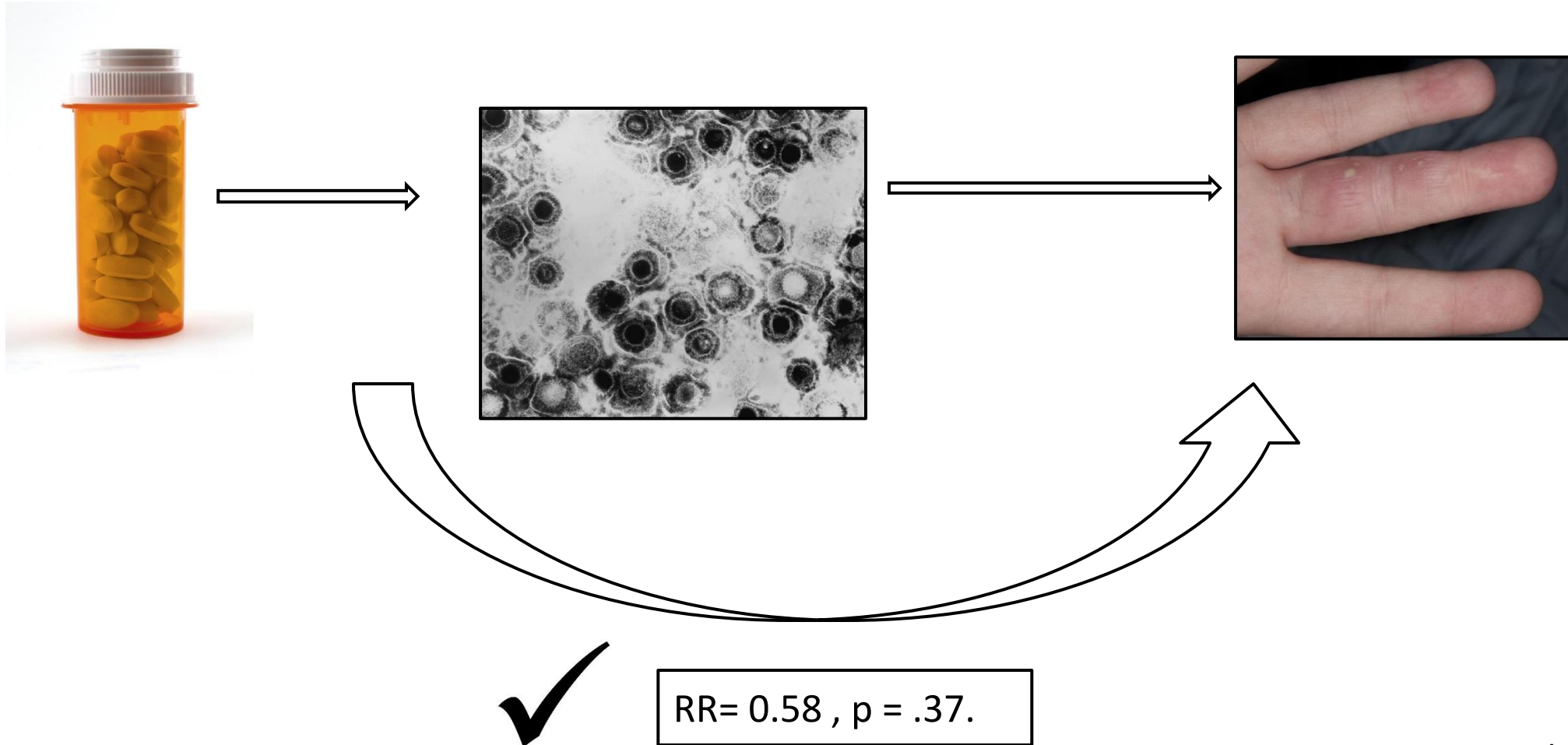
Pritelivir: risk of lesions, compared with placebo



RR= 0.13, p= 0.018

Wald et al, NEJM 2014
Agyemang et al JID 2018

Pritelivir: risk of recurrence, with shedding in the model



Agyemang et al JID 2018
Wald et al, NEJM 2014

Proportion of treatment (PTE) effect of pritelivir mediated via effect on viral shedding

- The lesion rate was 1.2% in pritelivir & 9.0% in the placebo
- the RR for lesions pritelivir vs placebo administration = 0.13 (95% CI .02–.70; $P = .018$)
- Shedding rate added to the model, the risk ratio for pritelivir increased to 0.58 (95% CI, 0.18–1.91; $P = .37$)
- an estimated PTE = 0.74: 74% of the effect of pritelivir on the genital lesion frequency was due to its effect on HSV shedding

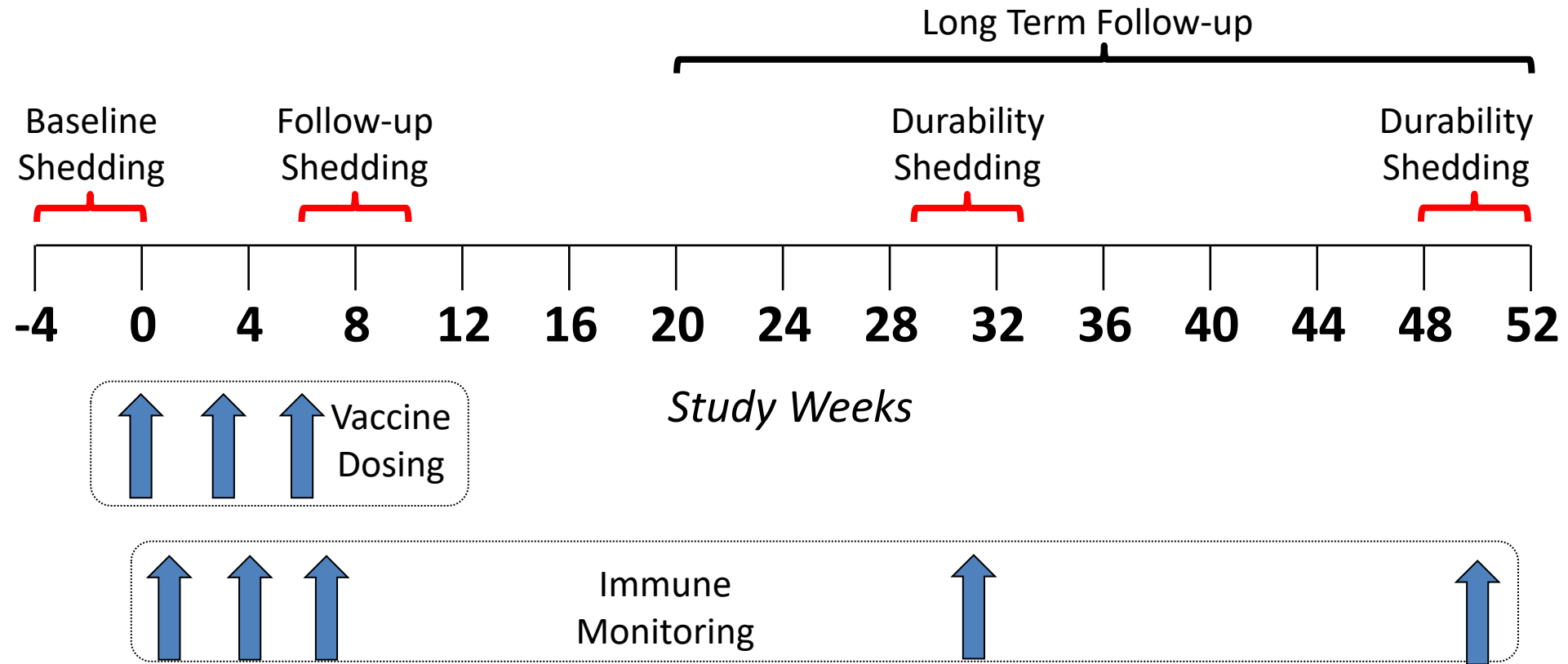
Effect of Pritelivir Compared With Valacyclovir on Genital HSV-2 Shedding in Patients With Frequent Recurrences

A Randomized Clinical Trial

Anna Wald, MD, MPH; Burkhard Timmler, MD; Amalia Magaret, PhD; Terri Warren, ANP; Stephen Tyring, MD, PhD; Christine Johnston, MD, MPH; Kenneth Fife, MD, PhD; Stacy Selke, MA; Meei-Li Huang, PhD; Hans-Peter Stoberneck, PhD; Holger Zimmermann, PhD; Lawrence Corey, MD; Alexander Birkmann, PhD; Helga Ruebsamen-Schaeff, PhD

- Randomized cross-over trial
- 98 participants
- Statistically significant superiority of pritelivir over valacyclovir for viral shedding, RR=0.42 (95%CI, 0.21 to 0.82; $P = .01$) and genital lesions (RR, 0.40 (95%CI, 0.17-0.96; $P = .04$).
- New antiviral agents can be developed
- Use of viral endpoints for evaluation of efficacy
- Regulatory implications

Therapeutic vaccine trial design using viral shedding as primary outcome





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SciVerse ScienceDirect

Current Opinion in
Virology

Maribavir and human cytomegalovirus—what happened in the clinical trials and why might the drug have failed?

Francisco M Marty¹ and Michael Boeckh²

Clinical Infectious Diseases

INVITED ARTICLE

IMMUNOCOMPROMISED HOSTS: David R. Snyderman, Section Editor



Use of Viral Load as a Surrogate Marker in Clinical Studies of Cytomegalovirus in Solid Organ Transplantation: A Systematic Review and Meta-analysis

Yoichiro Natori,¹ Ali Alghamdi,^{1,2} Mahmood Tazari,¹ Veronica Miller,³ Shahid Husain,¹ Takashi Komatsu,⁴ Paul Griffiths,⁵ Per Ljungman,⁶ Ani Orchanian-Cheff,⁷ Deepali Kumar,^{1,a} and Atul Humar^{1,a}; for the CMV Consensus Forum^b

Validation of plasma CMV viremia as a surrogate endpoint in antiviral studies

- viral loads in CMV disease are significantly greater than in asymptomatic viremia (OR, 9.3 95% CI 4.6–19.3)
- kinetics of viral replication are strongly associated with progression to disease
- incidence of CMV viremia and disease is significantly lower during prophylaxis:
 - viremia incidence: 3.2% vs 34.3%; $P < .001$
 - disease incidence: 1.1% vs 13.0%; $P < .001$
- treatment of viremia prevented disease
- viral load decline correlated with symptom resolution

Cytomegalovirus in Transplantation: Developing Drugs to Treat or Prevent Disease: Guidance for Industry May 2018

- “For other antiviral drugs (e.g., drugs for treatment of HIV, HBV, or HCV infection), proof of concept for antiviral activity generally is demonstrated via short-term administration of the investigational drug to chronically infected patients with measurable levels of circulating virus.”
- Pivotal efficacy trials: “The primary endpoint would be a composite endpoint defined as the occurrence of either tissue-invasive CMV disease or the development of CMV DNAemia above a prespecified threshold. It is expected that the endpoint will be driven by the incidence of CMV DNAemia. The FDA considers CMV viremia (DNAemia) as a sufficiently validated endpoint to grant traditional approval for NDAs for prophylaxis trials in HSCT recipients”

Conclusion & Caution

- HSV (mucosal shedding) or CMV (viremia) validated for clinical disease
- **Not** validated for sexual or perinatal transmission

Infections for which antimicrobials were approved based on surrogate markers of pathogen load

- HIV
- Hepatitis C
- Hepatitis B
- Hepatitis D
- CMV
- Tuberculosis (sputum culture conversion)

<https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure>;
accessed 14 October 2024

Acknowledgment

- Elfriede Agyemang
- Amalia Magaret
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- Josh Schiffer
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- Mei-Li Huang
- Alex Greninger
- Aicuris collaborators
- Michael Boeckh
- Elizabeth Duke