THE FORUM
For Collaborative Research℠

Collaborative Analyses: Lessons from Virlogy

Jeffrey Murray

Pilot Rx LLC

Berkeley Public Health

Disclaimer

- This presentation does not represent FDA opinions or advice.
- I am currently retired from FDA

Surrogate Marker Validation
from an FDA website*

- "Before a surrogate endpoint can be accepted in place of a clinical outcome, extensive evidence must accumulate, including evidence from epidemiological studies and clinical trials. Usually clinical trials are needed to show that the surrogate endpoint can be relied upon to predict, or correlate with, clinical benefit in a context of use. Surrogate endpoints that have undergone this extensive testing are called validated surrogate endpoints and these are accepted by the FDA as evidence of benefit."

*https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development

Relevant FDA Guidance

- "Expedited Programs for Serious Conditions – Drugs and Biologics,"-- May 2014, Procedural
- Discusses Evidentiary Criteria for Accelerated Approval: Use of a Surrogate Endpoint that is "Reasonably Likely" to predict Clinical Benefit
  - Depends on understanding of the disease process and the effect of a drug(s) on the disease process
  - Does not address the specific clinical evidence needed to support a conclusion that a particular surrogate endpoint is reasonably likely to predict clinical benefit because such evidence is case-specific and is not readily generalizable.
- After Accelerated Approval: Applicants are required to verify and describe the drug's clinical benefit where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit."
- Guidance does not address methods for clinical validation of a surrogate endpoint
- Guidance mentions HIV viral load as an example of a surrogate that predicts clinical benefit sufficient to support traditional approval (Next Slides)

HIV Drug Approval Using HIV-RNA as an Endpoint

- Prior to 1997, Confirmatory Clinical Endpoint studies were required after accelerated approval
- After 1997, HIV-RNA was considered validated endpoint
- HIV Clinical Endpoint was cumbersome
  - Endpoint = CDC criteria for an AIDS defining Event (20 various conditions) and death
  - Infections (viral, fungal, bacterial, parasitic, mycobacterial), syndromes (wasting), malignancies
  - Occurred at different levels of immune function, but in clinical trials weighted equally
  - Studies counted only first occurrence for most infections

Difficulties with Conducting Clinical Endpoint Studies after 1996

- Physicians and Study Participants unwilling to stay on randomized treatment after viral rebound and wait for clinical progression or even CD4 cell decline.
- Because ART (Active Antiretroviral Treatment) greatly reduced the incidence of clinical events, Clinical Endpoint Studies required very large patient numbers and would likely be confounded by treatment switches based on viral load changes.

HIV Endpoint Collaboration

- 1996 Surrogate Marker Working Group
  - Industry, academia, and government
- Commercial sponsors, FDA, NIH analyzed data to assess:
  - Correlations between viral load and clinical outcome
  - Correlations between short-term viral load suppression and durability of viral load response
- July 1997: Antiviral Advisory Committee to decide whether HIV-RNA was a validated endpoint (spoiler alert: yes)
- Multiple pooled analyses evaluated correlations of drug induced changes in HIV-RNA with clinical benefit

HIV-RNA and Clinical Benefit

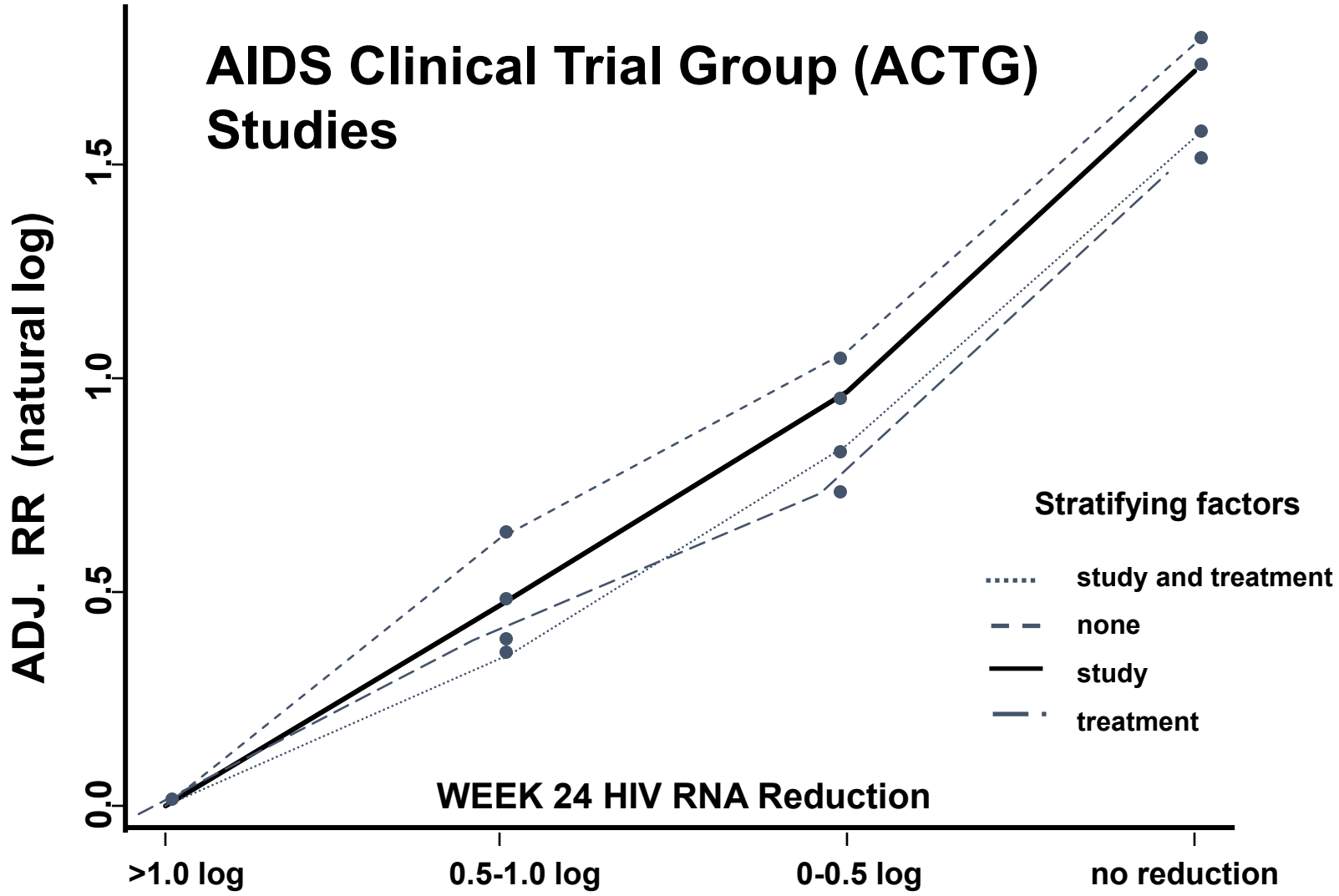
5 Analyses (1996), >5000 patients

ANALYSES	N	REGIMENS	CD4
1) Abbott Single Study (subset)	159	PI + NRTIS	21
2) NIH AIDS Clinical Trial Group Multiple Studies	1000	Many	218
3) Glaxo-Wellcome Studies Multiple Studies	1581	ZDV +3TC (others)	209
4) Pharmacia & Upjohn Studies: Two Studies	1842	DLV+ZDV DLV+DDI ZDV, DDI	230
5) Roche Study Single Study	940	SQV+DDC SQV, DDC	170

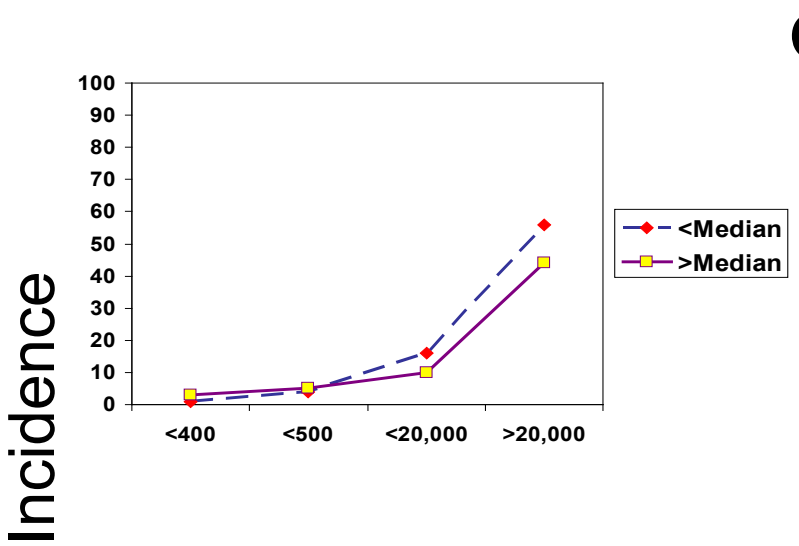
Association of Viral Load Reduction and Clinical Benefit

- Magnitude of HIV-RNA Reduction (log_{10} decrease)
- Nadir of HIV-RNA Reduction (thresholds, detection limits)
- Duration of HIV-RNA Reduction

Clinical Progression vs. HIV-RNA Reduction



Progression vs. Viral Load Nadir



Viral Load Nadir (copies/mL)

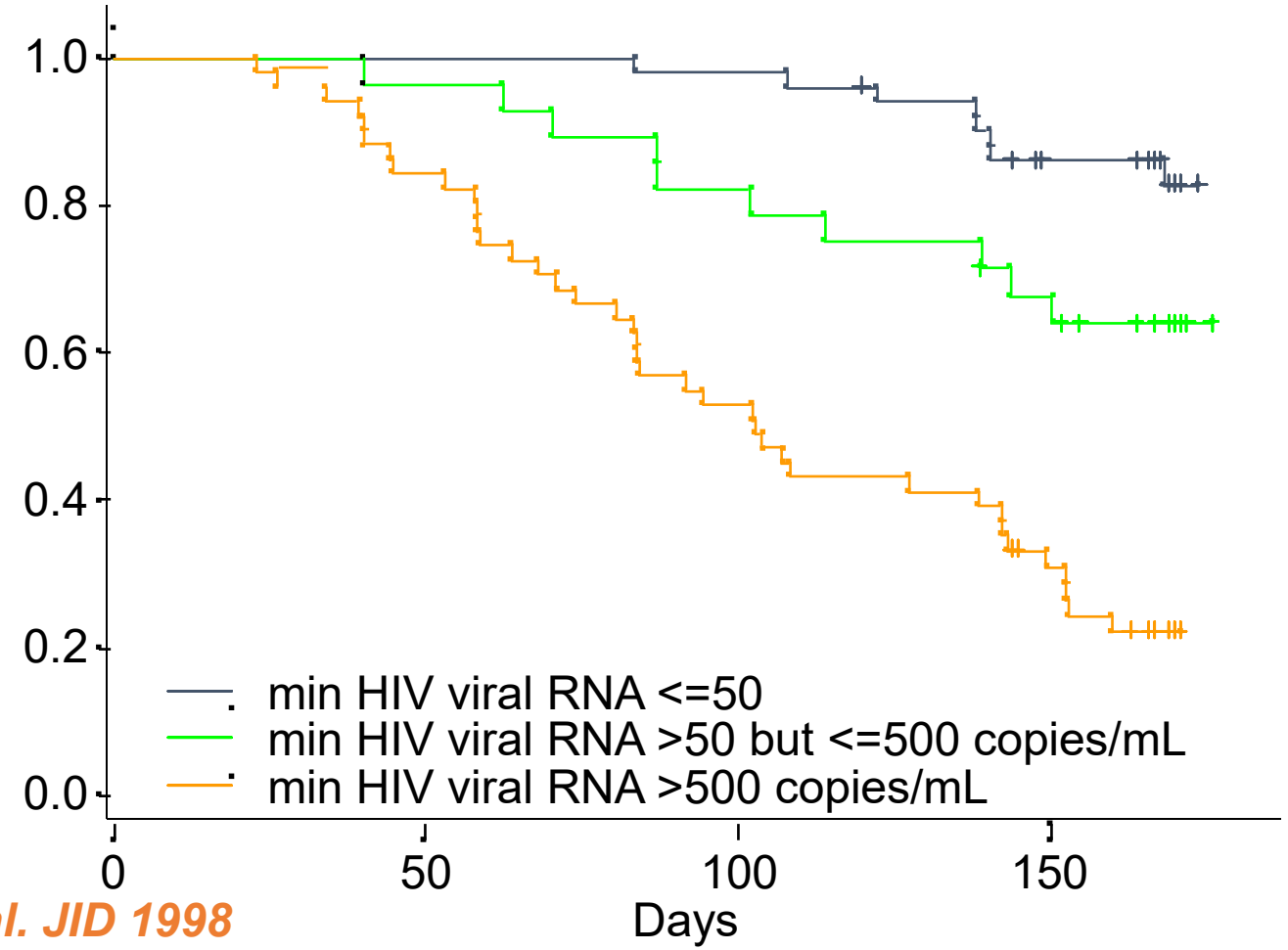
Clinical Hazard by Duration of Reduction

Pharmacia-Upjohn Analyses

Response Duration #DAYS	Hazard ratio	95% CI for HR
No response	1.000	
1-29	0.68	(0.43,1.04)
30-57	0.72	(0.41, 1.27)
58-113	0.55	(0.32, 0.95)
114-141	0.26	(0.128, 0.528)
>142	0.29	(0.145,0.564)

Sustained Suppression of vRNA by lowest vRNA Achieved

Merck Analyses



Drusano et al. JID 1998

Analyses: Summary of Findings

- HIV RNA decreases (> 0.5 log) are associated with lower risks of disease progression
- Greater Reductions associated with lower risks of progression
- More Sustained Reductions (> 8-12 weeks) in HIV RNA are associated with lower risks of disease progression
- Suppression of HIV-RNA below assay quantification is associated with longer duration of virologic suppression and less emergence of HIV resistance

HIV RNA: Clinical Correlations Fit with Biological Framework

- Greater Reductions in HIV RNA are associated with lower risks of disease progression.
- More Sustained Reductions in HIV RNA are associated with lower risks of disease progression
- Consistent with biologic theory/guidelines:
  - No HIV replication
  - No HIV mutations
  - No resistance
  - Durable response
  - Greater clinical benefit (disease “remission”)

Additonal Evidence Supporting Viral Load Endpoint

- Review of 13 clinical trials submitted to FDA
- SMART Study

13 Clinical Endpoint/Virology Studies

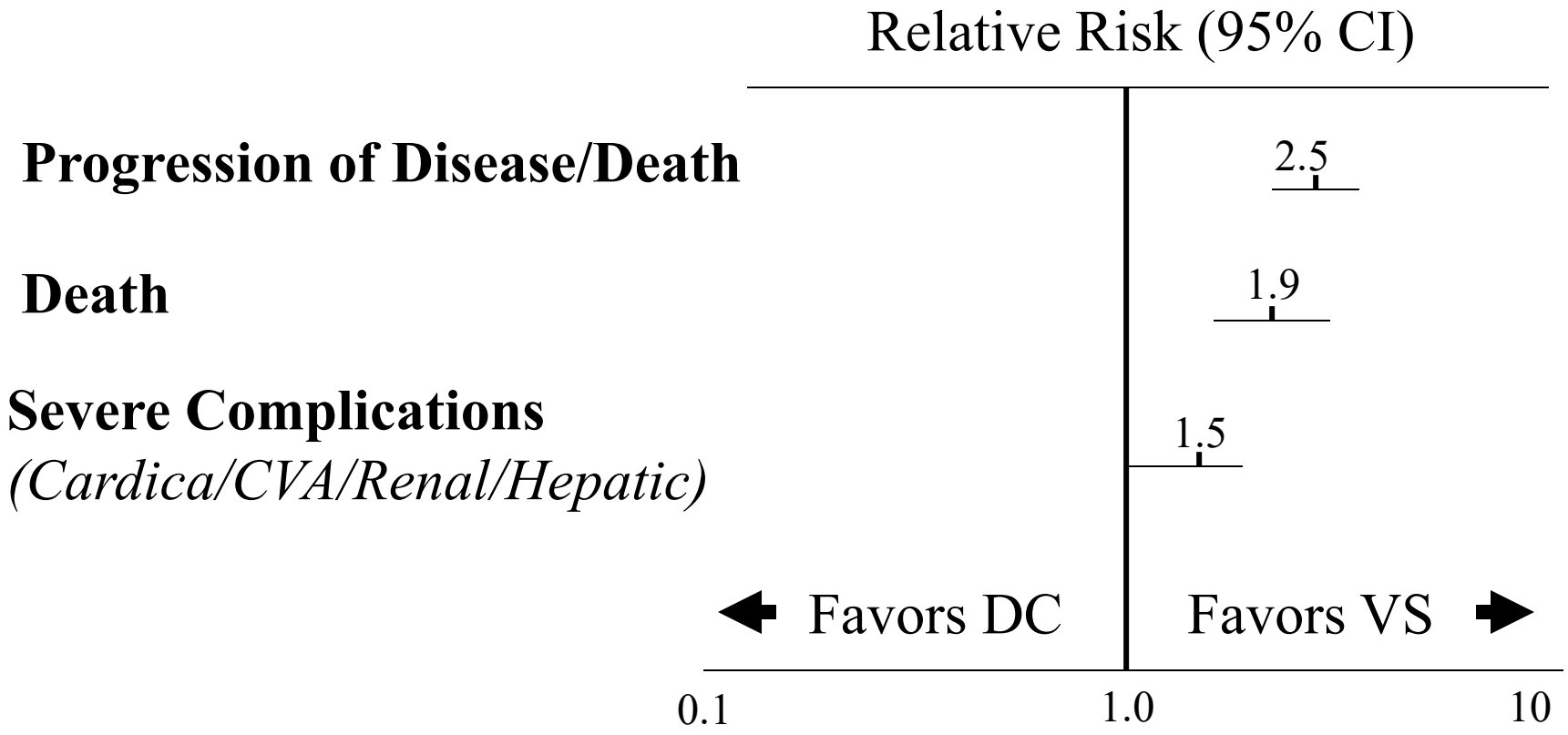
- VA Study (ZDV) -- + clinical effect (subset)
- ACTG 116B/117-- +clinical effect
- ACTG 175 (dual Nucs.) -- + clinical effect
- Delta (dual Nucs.) -- + clinical effect
- NV14256 (saquinavir) -- + clinical effect
- CAESAR (lamivudine) -- + clinical effect
- ACTG 300 (lamivudine) -- +clinical effect
- SV14604 (saquinavir) -- + clinical effect
- PU-0017 (delavirdine) -- no clinical effect
- M94-247 (ritonavir) -- + clinical effect
- ACTG 320 (indinavir) -- + clinical effect
- Study 028 (indinavir)-- + clinical effect
- ACTG 193 (nevirapine) -- no significant clinical effect

Every treatment arm with at least a 0.3-0.5 reduction in viral load compared to control also had a clinical benefit

SMART Study
Largest HIV Treatment RCT (n=5472)

- A strategy trials with two arms
- Drug Conservation (DC) vs. Viral Suppression (VS) group
- The DC group was treated based on CD4+ cell count-driven treatment interruptions in which ART was started (or restarted) below a CD4 count = 250 and stopped when CD4 rose above 350
- The VS group patients were started and maintained on treatment to maintain complete viral suppression

SMART Study Results



El Sadr W, et al. 13th CROI Abst 106LB. Feb 5-8. 2006

Other Infections: HCV, CMV

Viral Load Endpoints “Validated”

Chronic HCV Endpoint: Sustained Virologic Response (SVR)

- FDA Chronic HCV Guidance: “Multiple observational cohorts (cites 13 references) show correlations between SVR and improvements in clinical outcomes such as development of HCC, hepatic events, fibrosis, and all-cause mortality. These observational data support the use of SVR as a validated surrogate of HCV disease progression.”
- Simmons, Saleem et al. CID. 2015. “Long-Term Treatment Outcomes of Patients Infected With Hepatitis C Virus: A Systematic Review and Meta-analysis of the Survival Benefit of Achieving a Sustained Virological Response.” 31 studies (n= 33,360), mortality HR was 0.5 overall and 0.26 in cirrhosis subgroup.
- SVR was used as an endpoint for traditional approval prior to results of above cited meta-analysis or guidance; Major reason was that SVR was considered a virologic cure.

FDA Guidance, CMV Disease Post-Transplant Literature supports:

- CMV viremia predicts development of CMV disease in transplant recipients (Gor et al. 1998; Emery et al. 1999; Emery et al. 2000; Jang et al. 2012; Natori et al. 2018
- CMV viremia predicts mortality (Green et al. 2016).
- Prophylaxis or preemptive therapy for CMV viremia prevents CMV disease (Green et al. 2016)
- Suppression of viremia is associated with clinical resolution of CMV disease (Åsberg et al. 2007)
- CMV prophylaxis in HSCT recipients is associated with decreased mortality (Marty et al. 2017).

FDA Guidance, CMV Disease Post-Transplant

- “FDA considers CMV viremia (DNAemia) as a validated surrogate endpoint to be used as a part of a composite endpoint to support traditional approval. Therefore, traditional approval for new drug applications (NDAs) for CMV prophylaxis trials in HSCT recipients can be based on a composite endpoint defined as either the occurrence of tissue-invasive CMV disease or the initiation of anti-CMV preemptive therapy based on clinically significant CMV DNAemia.”
- Less supportive data than for HCV and HIV but the target population is much smaller and there were much fewer studies for CMV to analyze.