Surrogate Endpoints Example from HIV: From Clinical Endpoints to Viral Load

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Disclaimer

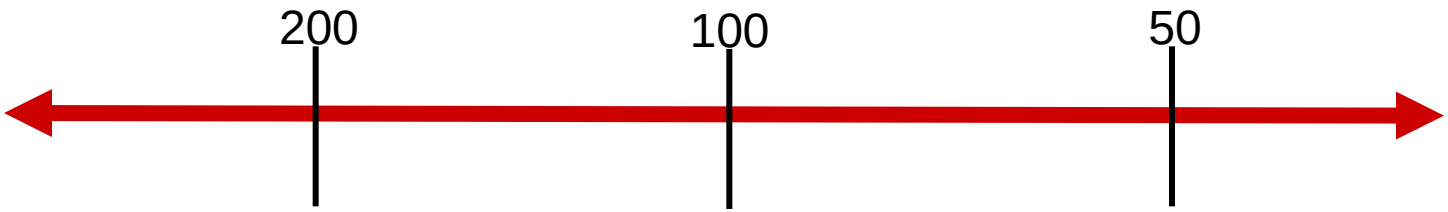
- The opinions and conclusions expressed in this presentation are those of the presenter and should not be interpreted as those of the FDA.
- I have no conflicts.
- Slides courtesy of Dr. Jeffery S. Murray from the Division of Antiviral Products

Clinical Endpoints

- AIDS-defining opportunistic infections (OI) and other conditions
  - Infections: viral, fungal, bacterial, parasitic, mycobacterial
  - Syndromes (wasting),
  - Malignancies
- Standard definitions established
- Usually first occurrence counted
- Events weighted equally, even if occur at different levels of immune function deficiency

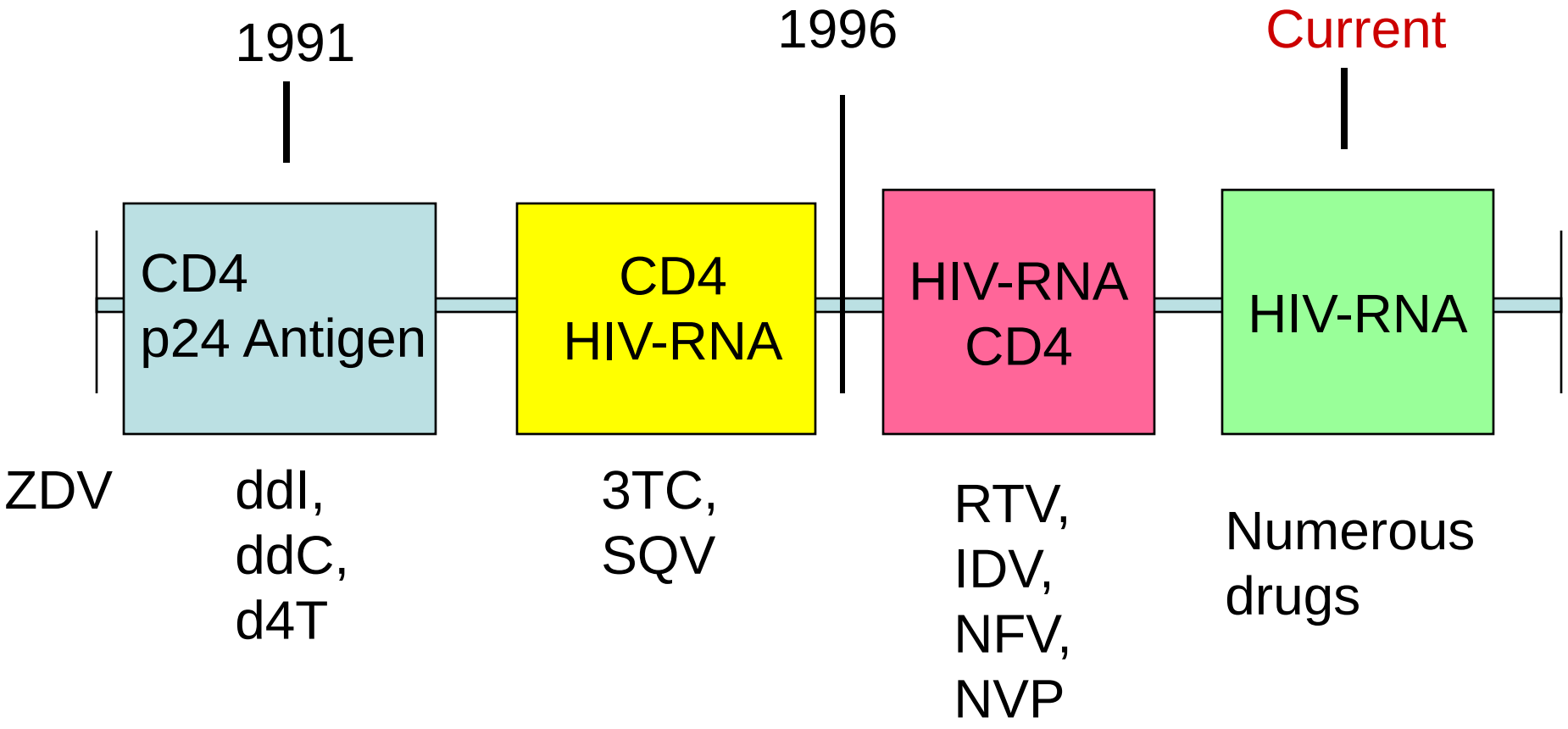
Clinical Endpoints

and Associated Peripheral Blood CD4+ Cell Count per µL



200	100	50
Tuberculosis	Pneumocystis	CMV retinitis
Recurrent Pneumonia	Toxoplasmosis	PML
Kaposi Sarcoma	Cryptococcus	MAC
Esophageal Candidiasis	Wasting	Lymphoma

Evolution of Surrogate Endpoints for HIV Drug Approval



Background: HIV-RNA (viral load)

- HIV Viral Load uses in 1996
  - Several assays available
    - lower limit of quantification 50-80 copies
  - Significant change (2 s.d.) = 3-fold or 0.5 log change
  - Prognostic indicator of disease progression, precedes CD4 cell decreases (CD4 better marker of net degree of immunosppression and criteria for starting treatment).
  - Used for assessing response to therapy
  - Viral rebound associated with drug resistance, signifies need to change regimen

Collaboration

- 1996 Surrogate Marker Working Group
  - Industry, academia, and government
- 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
  - Meta-analysis presented

HIV RNA and Clinical Benefit

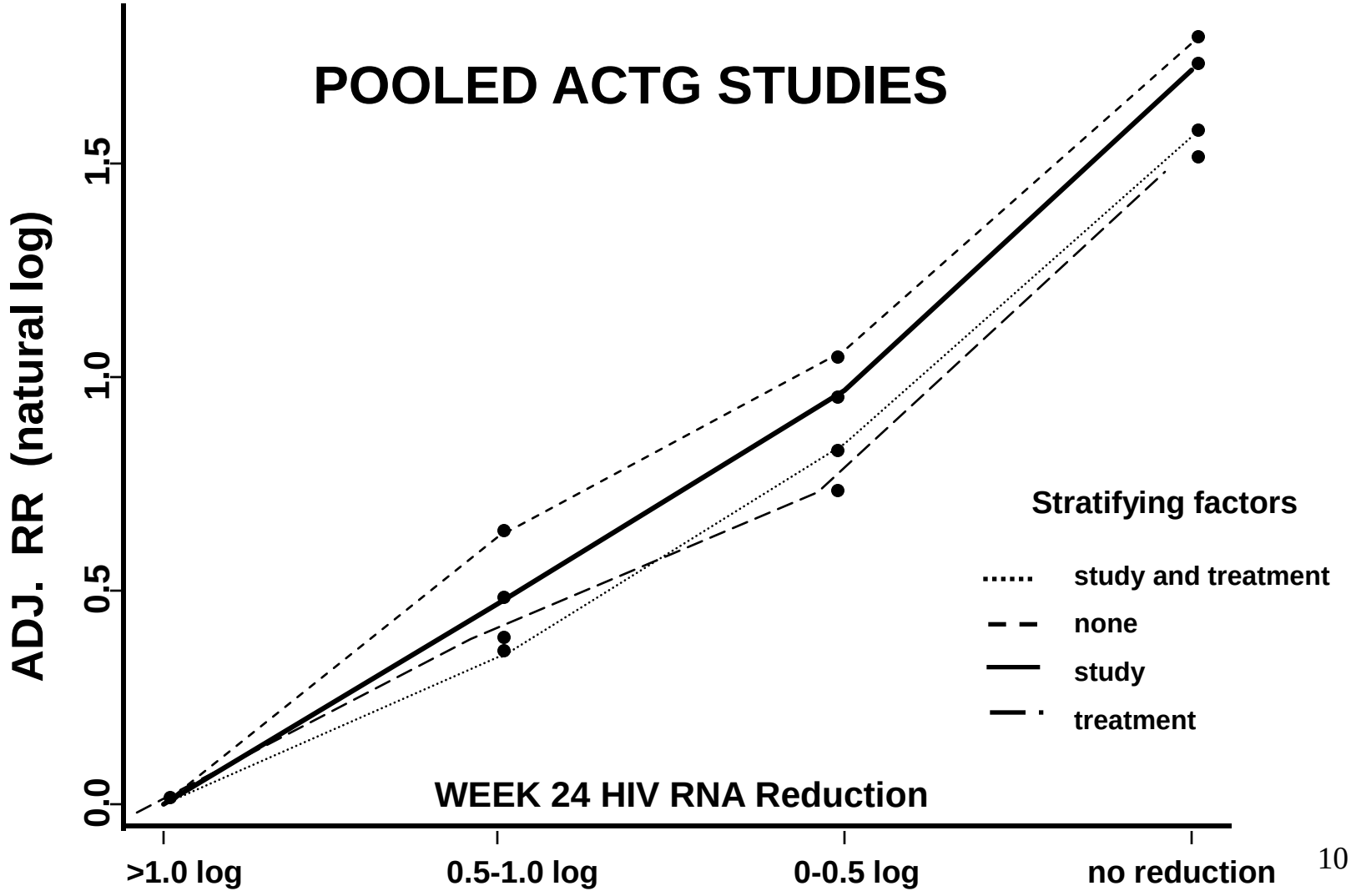
5 Analyses (1996), >5000 patients

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 (3 slides)

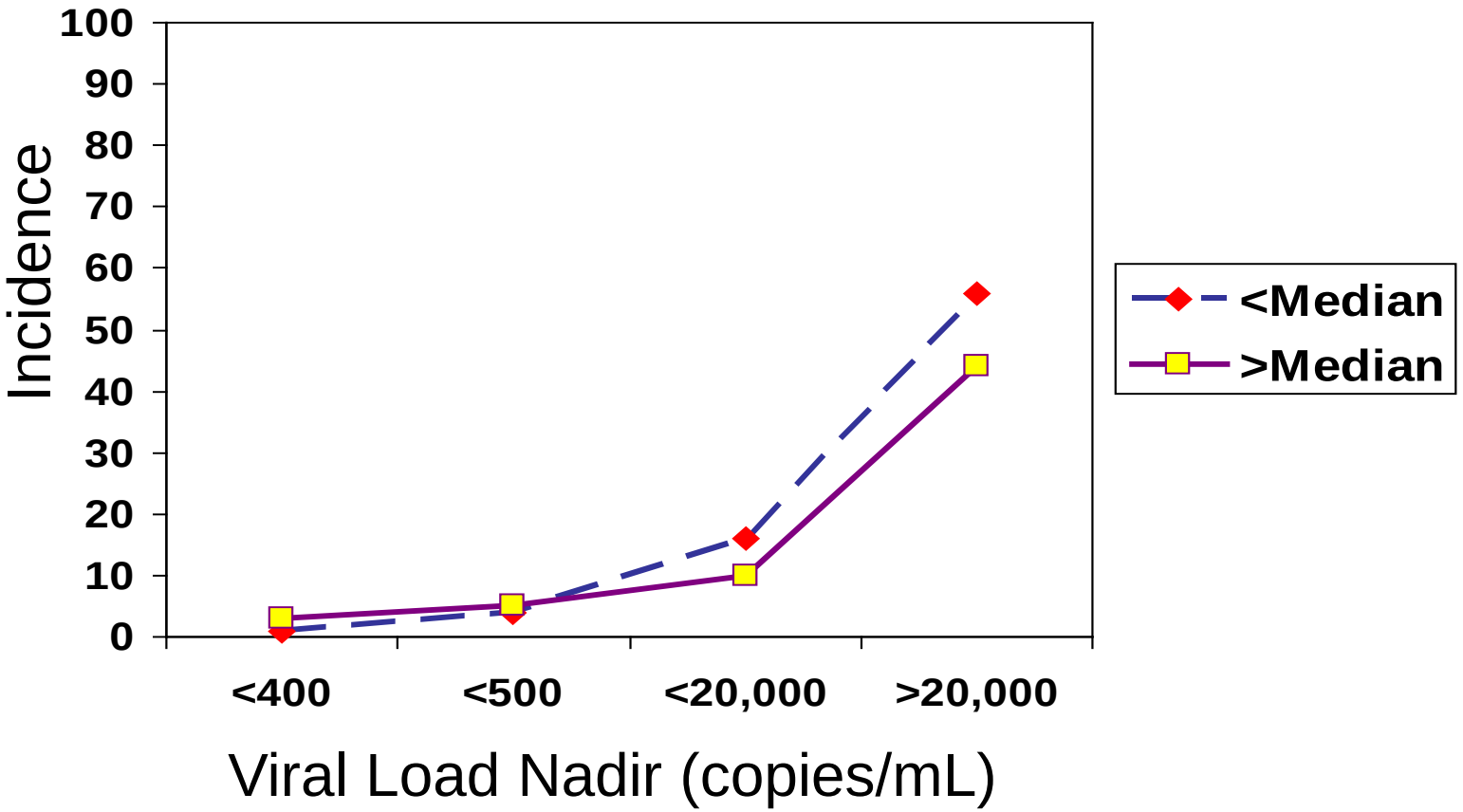
- Magnitude of Reduction
- Nadir of Reduction
- Duration of Reduction

Clinical Progression vs. HIV RNA Reduction



Progression vs. Viral Load Nadir

GSK Analyses



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)

Analyses: Summary of Findings

- There is lower risk of clinical progression associated with
  - HIV RNA decreases (> 0.5 log)
  - Greater reductions in HIV RNA
  - More sustained reductions (> 8-12 weeks)
- Suppression of HIV-RNA below assay quantification is associated with
  - longer duration of virologic suppression
  - less emergence of HIV resistance

July 1997 AC Meeting: Conclusions

- HIV RNA is a suitable endpoint for:
  - Accelerated Approval (24 weeks)..AND..
  - Traditional Approval (48 Weeks)
- Concordance with other markers (CD4)
- Precedents for “Lab” Endpoints:
  - Cholesterol and drugs for D.M.

Conclusions

- Validated surrogate endpoints can substantially facilitate drug development
- Multiple trials, large databases, and other types of supporting data are needed to “validate” a surrogate
- 100% correlation of a surrogate and clinical endpoint is not likely. Clinical Endpoints are not perfect gold standards
- There is room for improvement in enrolling and treating greater numbers of transplant patients under clinical protocols where these data can be collected

Selected References

- Murray JS, Elashoff MR, Iacono-Connors et al. The use of plasma RNA as a study endpoint in efficacy trials of antiretroviral drugs. *AIDS* 13, 797-804 (1999)
- FDA Guidance for Industry: Antiretroviral Drugs Using Plasma HIV RNA Measurements — Clinical Considerations for Accelerated and Traditional Approval (2002) http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070968.pdf