# CASE STUDY: HOW HIV VIRAL LOAD BECAME A SURROGATE AND THE IMPACT OF SHARING INFORMATION ON DRUG DEVELOPMENT

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# Presentation Outline

- Data Sharing and the Impact on Drug Development and Public Health
- Example #1:  HIV Viral Load
  - Background
  - Analyses
  - Impact
- Other Examples of Collaboration
  - HIV Resistance Testing
  - Metabolic Complications of HAART
- Conclusions

# Example #1:
# HIV Viral Load,
# Use as a Study Endpoint

# Background: HIV-RNA (viral load)

- HIV Viral Load: Clinical uses
  - Several assays with 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
  - Used for assessing response to therapy
  - Viral rebound associated with drug resistance, signifies need to change regimen

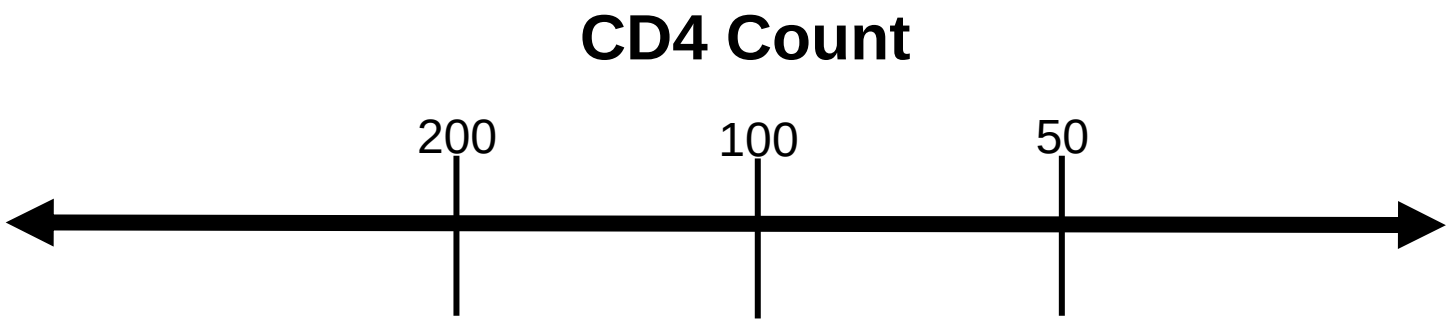
# HIV Drug Approval (up to 1997)

- Prior to 1997, Clinical Endpoint Studies Required for Traditional Approval of HIV drugs
  - CDC criteria for an AIDS defining Event (20) and Death
  - Accelerated Approval based on viral load and CD4 changes
  - Followed by Traditional Approval to verify and describe clinical benefit… where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit
- ISSUE: Physicians started changing treatments based on viral load. Participants less willing to stay on randomized treatment and wait for clinical progression. Clinical Endpoint Studies required large numbers and would likely be confounded by treatment switches.

# Clinical Endpoints

- Originally a case definition used more for epidemiologic purposes
- Approximately 20 different conditions
- Infections, syndromes (wasting), malignancies
- Infections: viral, fungal, bacterial, parasitic, mycobacterial
- Occur at different levels of immune function, but in clinical trials weighted equally
- Studies counted only first occurrence for most infections

# Clinical Endpoints




| | | |
|---|---|---|
| Tuberculosis | Pneumocystis | CMV retinitis |
| Recurrent Pneumonia | Toxoplasmosis | PML |
| Kaposi Sarcoma | Cryptococcus | MAC |
| Esophageal Candidiasis | Wasting | Lymphoma |

# Collaboration Example #1

- 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

# Barriers to Collaboration

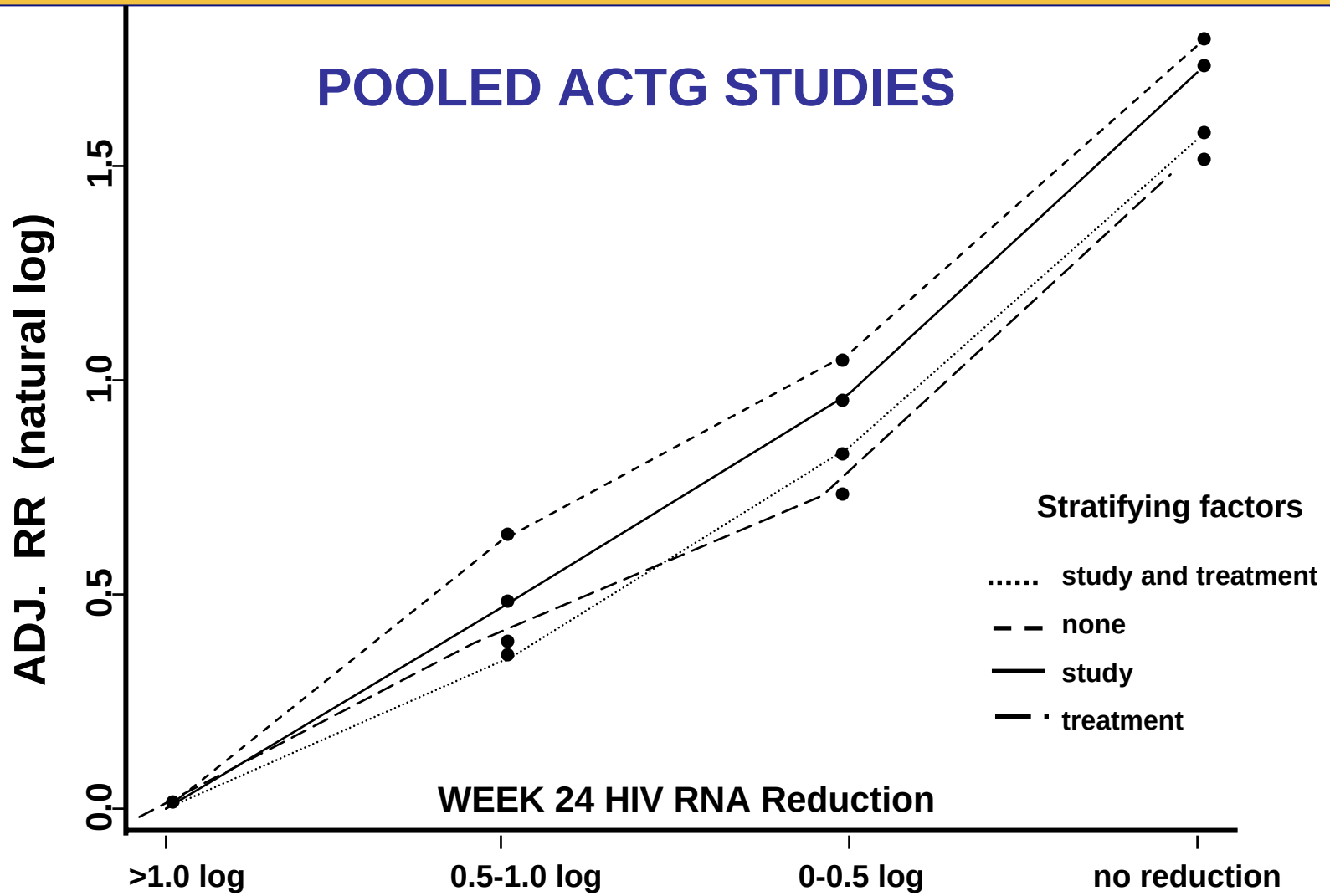
- Legal/proprietary issues related to data transfers between companies
- Interim Solution:
  - Each Company submitted data in agreed upon format to FDA
  - Each Company presented followed by FDA presentation

# HIV RNA and Clinical Benefit

## 5 Analyses (1996), >5000 patients

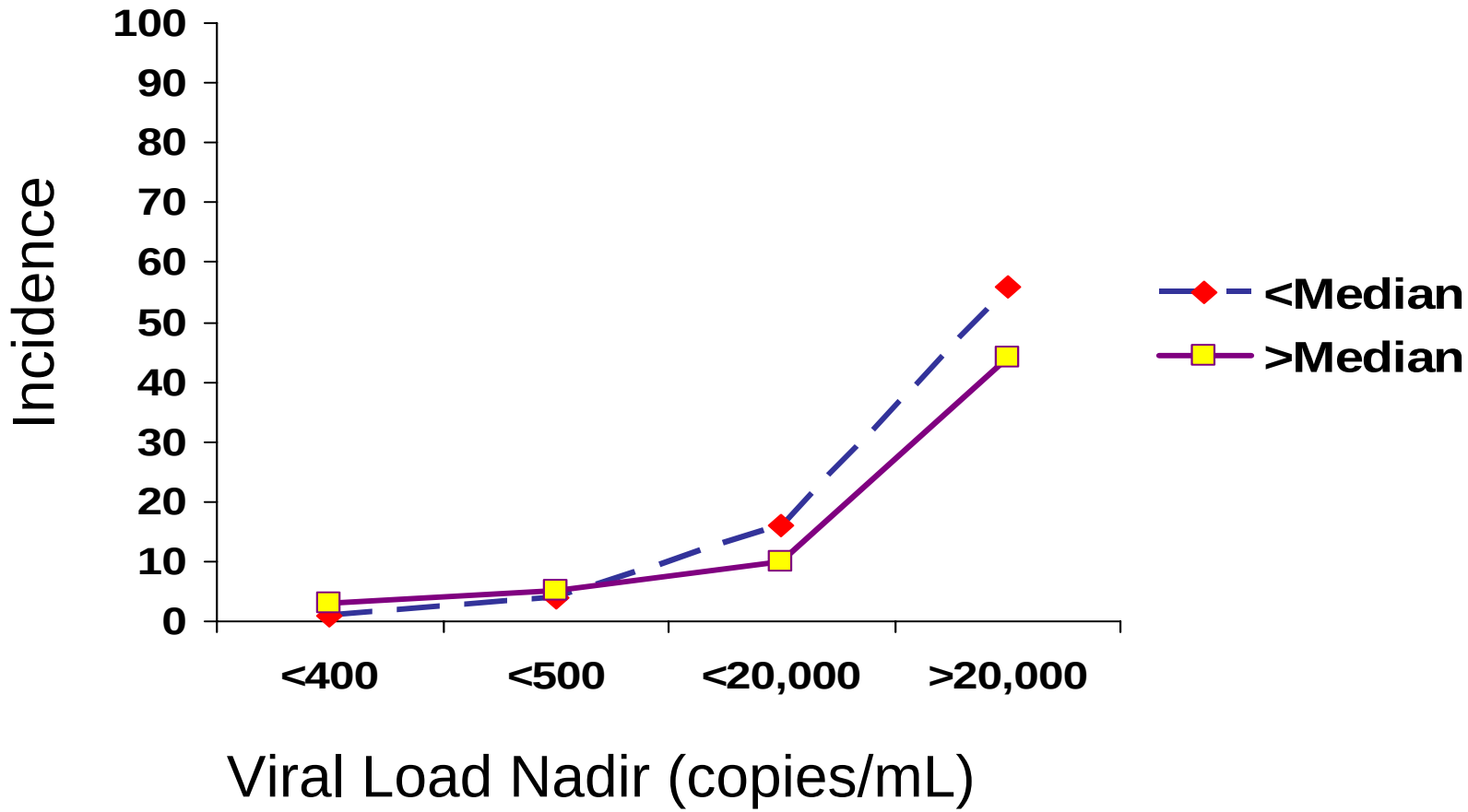
| ANALYSES | N | REGIMENS | CD4 |
|---|---|---|---|
| 1) Abbott<br>Single Study (subset) | 159 | PI + NRTIS | 21 |
| 2) NIH AIDS Clinical Trial Group<br>Multiple Studies | 1000 | Many | 218 |
| 3) Glaxo-Wellcome Studies<br>Multiple Studies | 1581 | ZDV +3TC<br>(others) | 209 |
| 4) Pharmacia & Upjohn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

# Clinical Progression vs. HIV RNA Reduction



# Progression vs. Viral Load Nadir

## GSK Analyses



# Clinical Hazard by Duration of Reduction

## Pharmacia-Upjohn Analyses

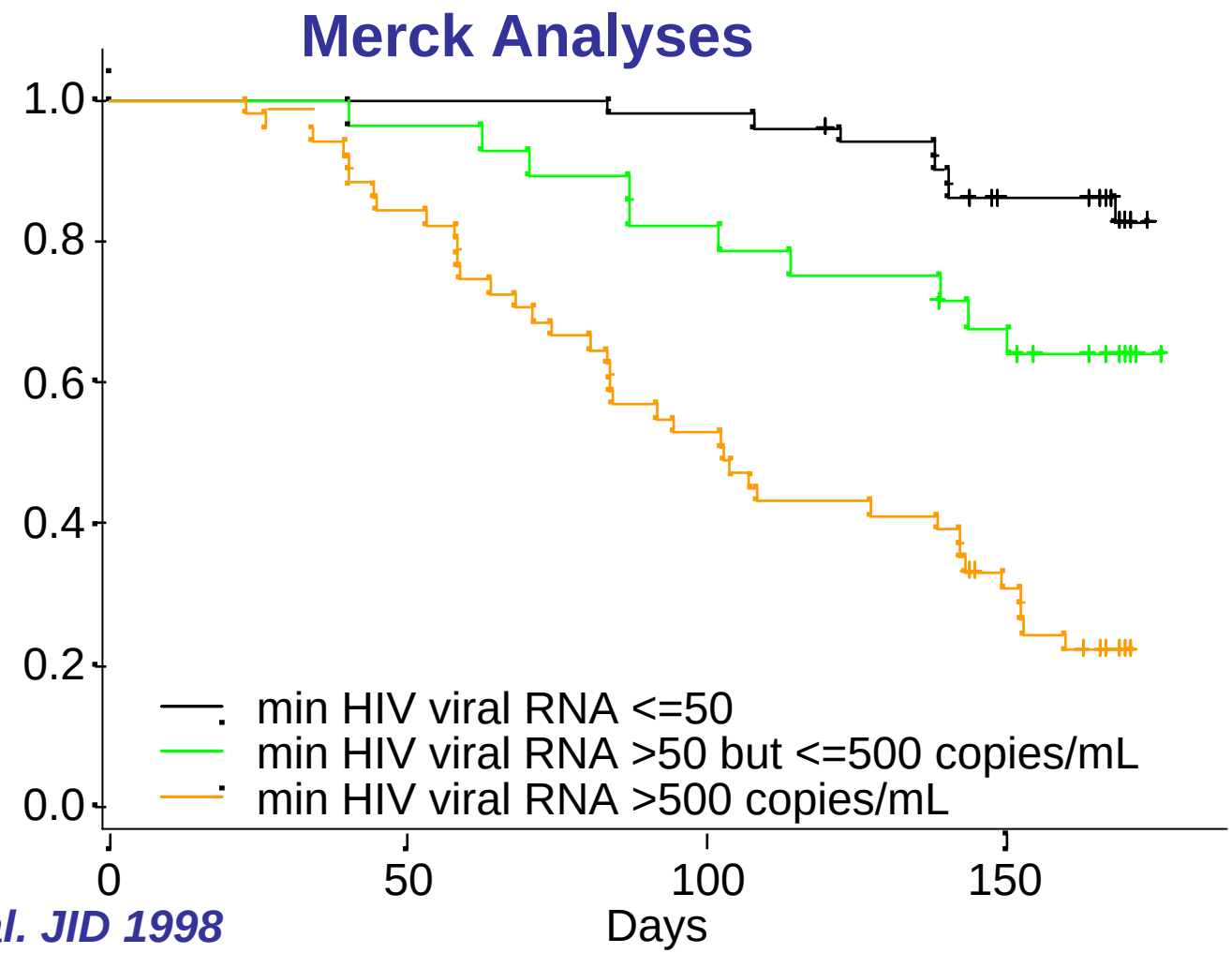
| Response Duration #DAYS | Hazard ratio | 95% CI for HR |
|---|---|---|
| No response | 1.000 | |
| 1-29 | 0.68 | (0.43,1.04) |
| 30-57 | 0.72 | (0.41, 1.27) |
| 58-113 | 0.55 | (0.32, 0.95) |
| 114-141 | 0.26 | (0.128, 0.528) |
| >142 | 0.29 | (0.145,0.564) |

# Virologic Durability Analyses

DATA SOURCES

- Merck
- Agouron
- Boehringer Ingelheim
- Glaxo

# Sustained Suppression of vRNA by lowest vRNA Achieved




*Drusano et al. JID 1998*

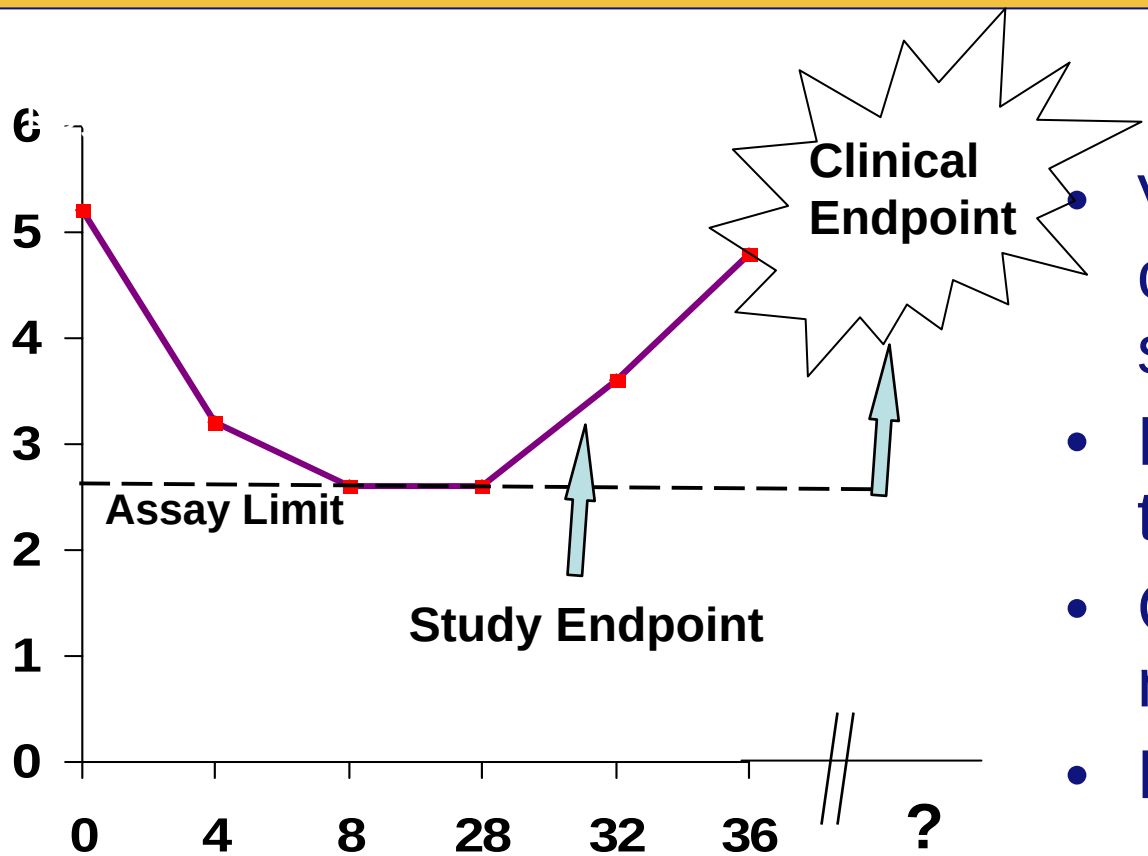
# Analyses: Summary of Findings

- 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

# July 1997 AC Meeting: Conclusions

- HIV RNA is a suitable endpoint for:
  - Accelerated Approval (24 weeks)..AND..
  - Traditional Approval (48 Weeks)
- Clinical Endpoint Studies Remain an Option (= CDC AIDS defining Events)
- Concordance with other markers (CD4)
- Precedents for “Lab” Endpoints:
  - Cholesterol and drugs for D.M.

# Advantages for Clinical Trials




- Virologic Endpoint captured before Rx switches
- Less confounding due to treatment switches
- Coincides with clinical management
- Participant Acceptance

# Ex. #1: Impact

- Greatly expedited HIV drug development (a dozen new drugs approved in 10 years)
  - Smaller, shorter trials
  - Improved acceptability for participants
  - Kept HIV pipeline abundant
- Helped FDA to write Guidance document
- Resulted in publications
- Created an unprecedented collegial relationship among sponsors

# Other Examples of Collaboration in HIV Drug Development

# Example #2: HIV Resistance Testing

- Issue:
  - HIV Resistance Testing data not adequately represented in product labeling.
  - FDA concerned about limitations of tests and clinical relevance of in vitro resistance
- Collaboration:
  - Modeled after Surrogate Marker working group
  - Industry, academia, government, community
  - Initiated by GSK

# Ex. #2: HIV Resistance

- Identified ongoing studies and sponsor data sources
- Developed standardized methods for analyzing correlations between HIV resistance and clinical outcomes
- Analyses presented at a 1999 Antivirals Advisory Committee Meeting
- Goal: to demonstrate clinical relevance of HIV resistance testing to clinical/virologic outcomes to support inclusion of resistance data in product labeling

# Description of Re-analyzed Studies

| Study Name | ABC Pooled | ACTG 333 | ACTG 364 | ACTG 372 | CNAA 2007 |
|---|---|---|---|---|---|
| Investigator | R. Lanier | M. Para | D. Katzenstein | S. Hammer | M. Ait-Khaled |
| N with GT/PT | 134 / 84 | 46 / 0 | 144 / 0 | 96 / 80 | 94 / 64 |
| Treatment Experience | nRTI exp, PI/NNRTI naïve | nRTI/SQV exp, naïve to other PIs | Heavily nRTI exp, naïve to PI/NNRTI | Heavily nRTI exp, IDV exp | Heavily nRTI/ PI exp, 42% NNRTI exp |
| Resistance Technology | GT (ABI) PT (Virco) | GT (ABI/ clonal seq) | GT (Stanford) | GT (Virco) PT (Virco) | GT (ABI) PT (Virco) |
| Median Baseline HIV RNA (range) [25$^{th}$ – 75$^{th}$] | 3.7 (2.6 – 5.8) | 4.1 | 4.1 [3.6 – 4.6] | 4.6 | 5.1 (3.4 - 6.6) |
| Median Baseline CD4 (range) [25$^{th}$ – 75$^{th}$] | 417 (11– 1266) | 240 | 323 [242 – 460] | 196 | 160 (10 -782) |

# Description of Re-analyzed Studies

| Name | Stanford | BC Centre | Frankfurt | Swiss | GS 408 |
|---|---|---|---|---|---|
| Investigator | A. Zolopa | R. Harrigan | V. Miller | S. Yerly | M. Miller |
| N with GT/PT | 54 / 0 | 58 / 53 | 0 / 50 | 62 / 0 | 161 / 0 |
| Treatment Experience | Heavily nRTI/PI exp | nRTI exp, NNRTI naïve | Heavily pretreated | HAART "failures" | Heavily pretreated |
| Resistance Technology | GT (Stanford) | GT (Virco)<br>PT (Virco) | PT (Virco) | GT (ABI) | GT (Pharmacia) |
| Median Baseline HIV RNA (range) [25th – 75th] | 5.0 | 4.8 (2.7 – 5.8) | 5.5 | 5.2 (3.1 – 6.4) | 4.1* |
| Median Baseline CD4 (range) [25th – 75th] | 245 | 160 (10 - 560) | 95 | 113 (4 – 633) | 338* |

*Mean Values

# Summary of Key Points

- Standardized re-analysis of retrospective studies generally confirms associations between baseline genotype or phenotype and virologic response
  - small datasets → variability (broad CIs)
- Prospective, intervention-based trials support the clinical value of resistance testing for selection of treatment regimens in experienced patients
- Data accumulating from ongoing clinical trials of approved and investigational agents will refine the interpretation and improve the predictive value of specific resistance test results

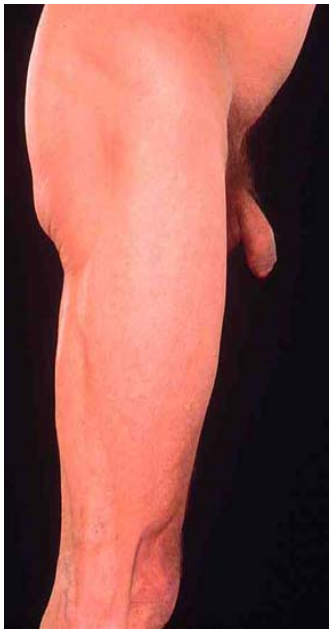
# Ex. 2: Impact

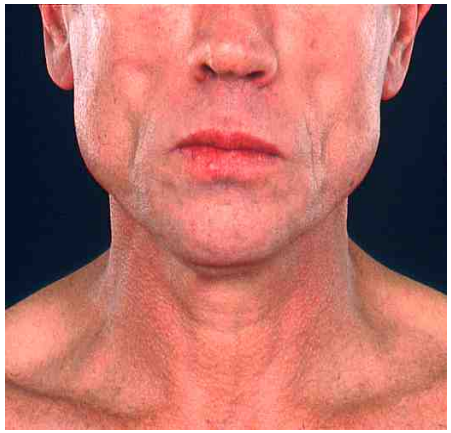
- HIV resistance testing is part of routine practice
- Studies of clinical resistance increased dramatically
- Amount of resistance data included in the product labeling increased and of value for clinical decision making.

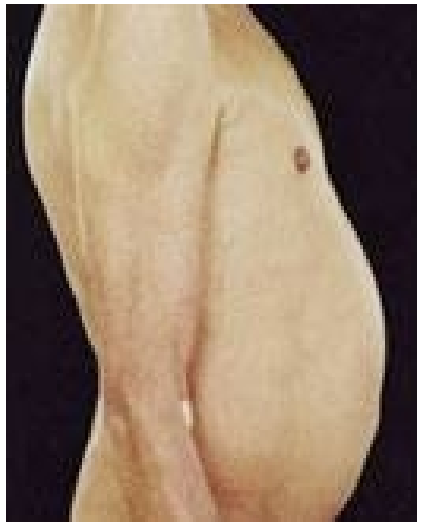
# Example #3 Metabolic Complications

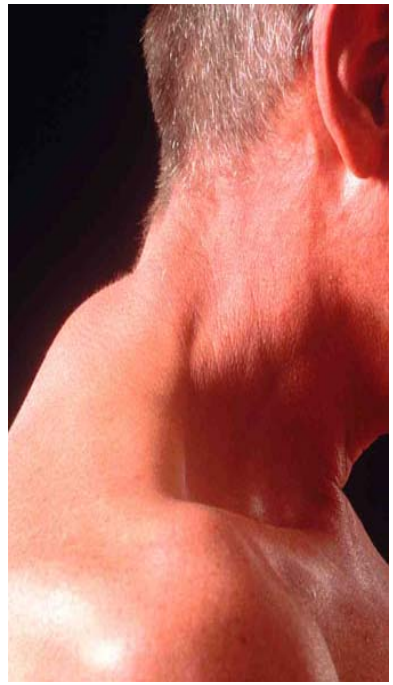
- Issue: Will HAART increase cardiovascular risk (MI, stroke, death)?
  - EMEA posed question to sponsors
  - Lipodystrophy and lipid abnormalities associated with HAART
- Collaboration:
  - Multiple Application Holders with academic and government consultation
  - Funded 2 large cohorts to evaluate potential safety risks

# HIV-Associated Fat Redistribution









# Evaluation of CV Risks

- Safety Signal with Biologic Plausibility
- Request from EMEA to Industry
- What is the risk for CV disease with HAART?
- Cohort Studies: sponsored by Industry Collaboration
  - VA Study--U.S.
  - DAD Study--Europe

# Ex. 3: Results of Collaboration

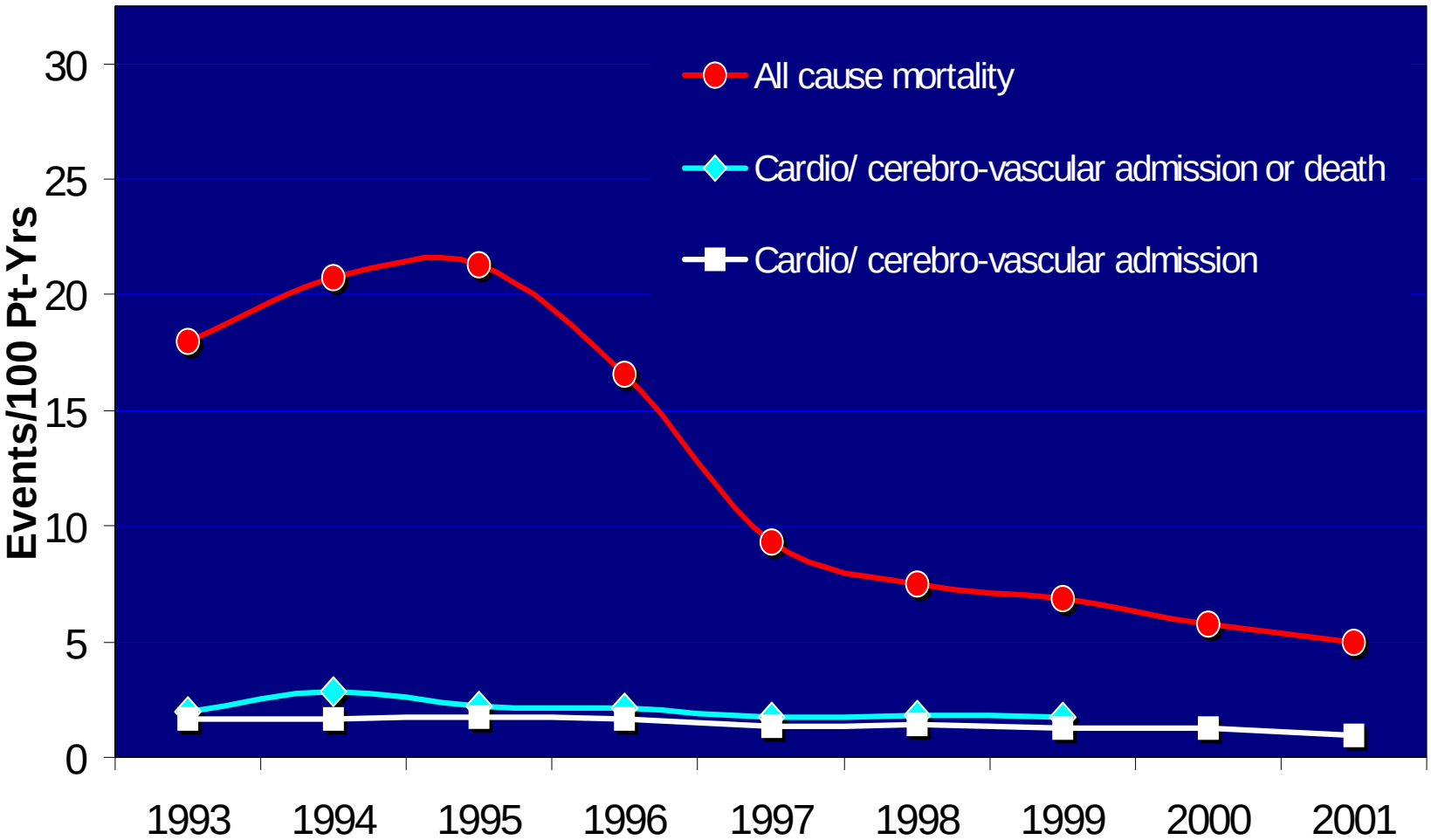
ORIGINAL ARTICLE

## Cardiovascular and Cerebrovascular Events in Patients Treated for Human Immunodeficiency Virus Infection

Samuel A. Bozzette, M.D., Ph.D., Christopher F. Ake, Ph.D., Henry K. Tam, Ph.D., Sophia W. Chang, M.D., M.P.H., and Thomas A. Louis, Ph.D.

N Engl J Med 2003;348:702-10

# VA Study: Outcomes



# D:A:D Study: Cohorts

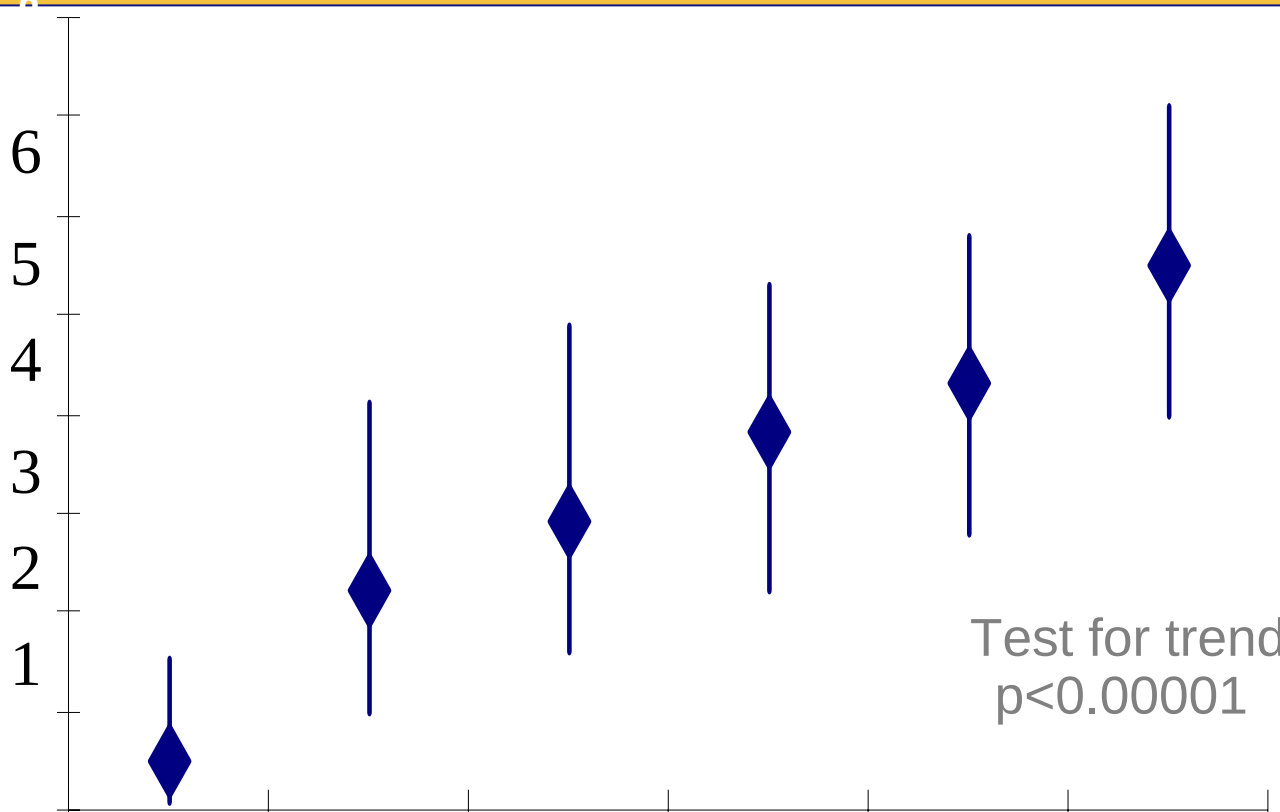
- ATHENA (Netherlands)
- AHOD (Australia)
- Aquitaine (France)
- BASS (Spain)
- Brussels St.Pierre
- CPCRA (USA)
- EuroSIDA (Multinational)
- HivBIVUS (Sweden)
- ICONA (Italy)
- Nice
- SHCS (Switzerland)

# Combination Antiretroviral Therapy and the Risk of Myocardial Infarction

*The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group*

**NEJM: Volume 349:1993-2003 November 20, 2003**
**Number 21**

# DAD Study: MI by HAART exposure




| Yrs. on HAART | None | <1 | 1-2 | 2-3 | 3-4 | 4-5 | Total |
|---|---|---|---|---|---|---|---|
| No. MIs | 3 | 9 | 14 | 22 | 31 | 47 | 126 |
| No. PY | 5,714 | 4,140 | 4,801 | 5,847 | 7,220 | 8,477 | 36,199 |

# Ex. #3: Results/Impact

- Showed that benefits of HAART still outweighed risk of CV
- Indicated possible increase risk of CV disease
- Encouraged more aggressive clinical management of lipid abnormalities and other modifiable CV risks
- Funded important cohorts that are now being used to assess other safety questions such as liver toxicity risks

# Conclusions

- Multiple Examples of Collaboration in HIV Drug Development
  - Reasons:  Drugs used in combination, chronic treatment, sequential regimens
  - Public Health Commitment/Community Input
- Resulted in Expedited Evaluation of Efficacy
- Labeling changes for Resistance and Safety Concerns
- Guidance Documents and Publications