

# **Surrogate endpoints in** **HIV/AIDS clinical trials**

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# Clinical Endpoint Definition

- A characteristic or variable that reflects how a patient feels, functions or survives
- Except for survival, others [how a person feels or functions] involve some sort of intermediary measurement and may not be appropriate
  - Laboratory tests
  - Quality of life
  - Co-Morbidities: type

# Surrogate Marker

## Working Definition

A laboratory or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and that is expected to predict clinical benefit or lack of benefit following treatment, therapy or intervention

# **Biomarker: Definition**

- **A parameter that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention**
- **US FDA has provided lists of possible, probable and known valid biomarker categories depending on available scientific information**

# Hierarchy/ preference for selecting outcome measures

- True Clinical Efficacy Measure
- Validated Surrogate Endpoint
- Non-validated Surrogate Endpoint that is “reasonably likely to predict clinical benefit”
- Correlate that is solely a measure of Biological Activity

...Fleming (2005), *Health Affairs*

# **Validation of Surrogate Endpoints**

## **Statistical**

Meta-analyses of clinical trials data: It is important to assess more than a single study to decide on the adequacy of a surrogate

## **Clinical**

1. The surrogate must be in the causal pathway of the disease process
2. An intervention's entire effect on the clinical outcome of interest should be fully captured by the surrogate

# **When is the use of surrogate endpoints justified?**

- **Can be measured earlier: reduce the size and duration of the trial**
  - CD4 count slope Vs mortality**
- **Convenient, less expensive or less invasive**
  - VIA Vs colposcopy or biopsy for diagnosis of cervical cancer in HIV infected women**
- **Can be measured more frequently**
  - CD4 counts every 3-6 months to identify treatment failure in trials involving ART**

# Range of clinical trials in HIV/ AIDS

- Therapeutic trials
- Preventive trials
- Program evaluation trials
- Evaluation of diagnostics

# **Factors influencing various end-points in HIV/ AIDS in clinical trials**

- Individual Vs Community based trials
- Healthy volunteers Vs HIV infected persons Vs AIDS patients
- Safety Vs Immunogenicity Vs Efficacy trials

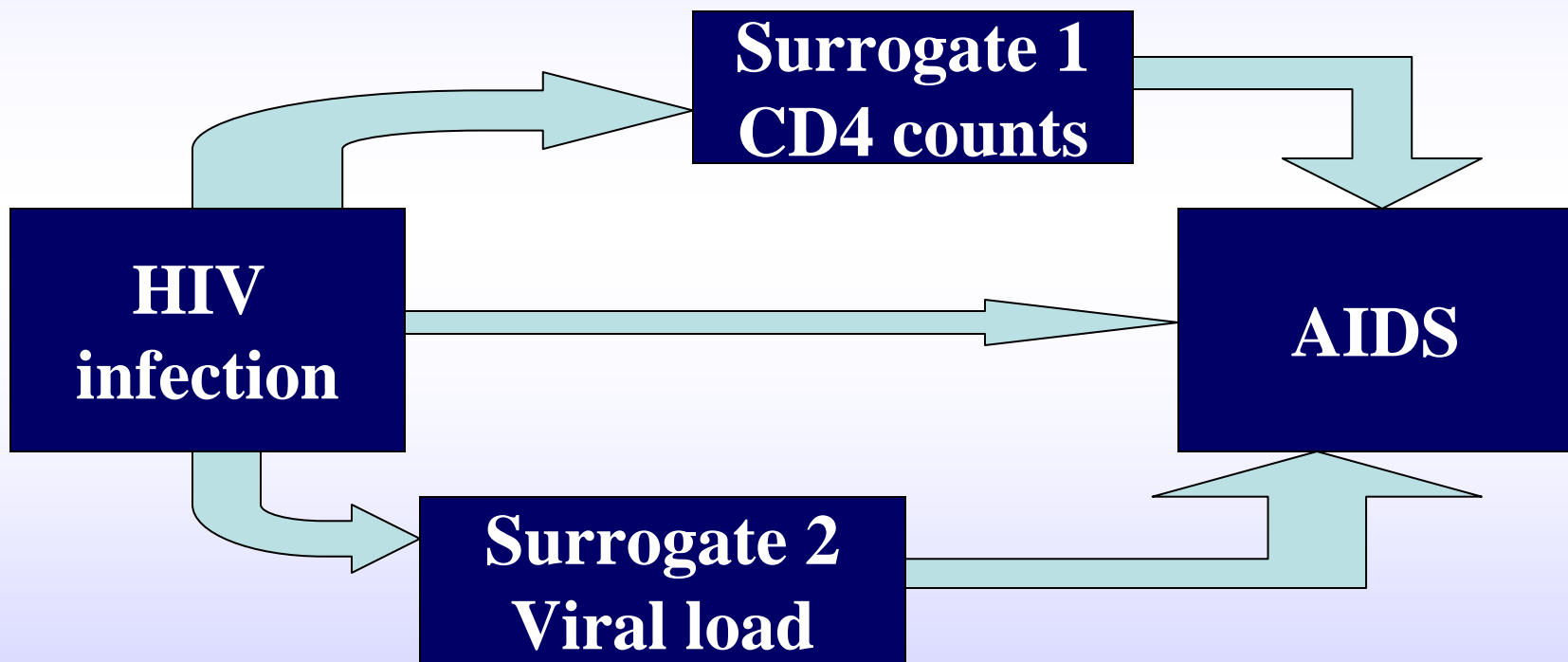
# Endpoints used in HIV/ AIDS Clinical Trials

- A *clinical outcome*: e.g. HIV infection or AIDS defining illness or death
- A *surrogate endpoint* only predicts the outcome: e.g. CD4 counts
- A *mixed surrogate/ clinical benefit endpoint* directly measures significant benefit to patient and also predicts an additional, more substantial benefit to patient: e.g. viral load

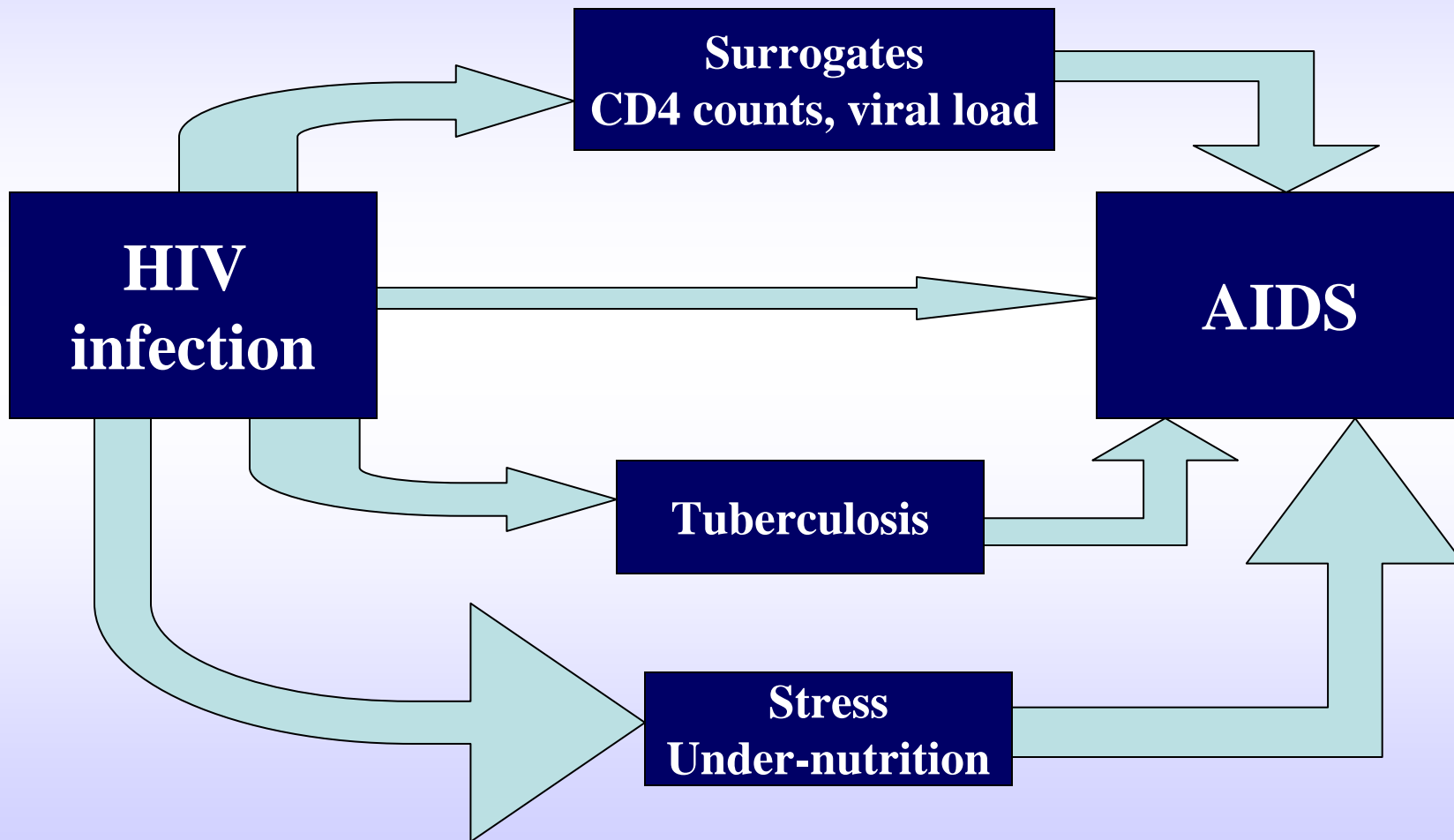
- **Caution in using surrogate endpoints:**

- Using biological markers as a surrogate endpoint, one may obtain misleading false positive or false negative conclusion when assessing treatment effects of longer term clinical outcome

# Significance of surrogates with respect to clinical outcome in AIDS



# Significance of other biological processes in AIDS



# An example of possible problems in interpreting surrogate endpoints in HIV

Treatment decided based on effect on surrogate marker	<b>CD4 counts as surrogate marker</b>	Surrogate may be a strong predictor of outcome
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Treatments may also affect biological processes	<b>Biological processes: Various opportunistic infections</b>	Biological processes can affect the outcomes
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# **CD4 count as SEP in HIV trials**

- **CD4 lymphocyte count widely used and accepted as a SEP for progression to AIDS**
- **ZDV approved in 1987 based on 17 weeks survival**
- **ddI approved in 1991 based on surrogate endpoint (CD4) with limited indication (in AZT failures)**
- **ddC is the first drug approved under accelerated approval regulation (1992) and more than 12 other HIV drugs has been approved under this regulation since then.**

# The Concorde Trial .. 1

- **1749 asymptomatic HIV-positive patients were randomly assigned to receive immediate or deferred treatment with AZT.**
- **In 3 years follow-up, the decline in CD4 cell counts was slowed by immediate zidovudine therapy, [Difference of 30 to 35 cells/mm<sup>3</sup> between the two treatment groups].**
- **Patients in deferred treatment arm more quickly achieved a 50% decline in CD4 cell counts.**

# **The Concorde Trial .. 2**

- **But, the clinical outcomes did not reflect these changes. Time of progression to AIDS-related complex, AIDS, or death was essentially similar in two arms.**
- **Benefit of early initiation of AZT treatment based on surrogate endpoint would have been a false positive conclusion**
- **The pressures to use zidovudine treatment in asymptomatic persons with HIV were not supported by these longer-term clinical events.**

# **Viral load as a surrogate endpoint**

**Benefit of treatment partially, but not fully, mediated through viral load.**

**Other factors: viral fitness, resistance, toxicity, presence of HIV in compartments besides plasma do affect therapeutic benefits.**

**For trials comparing highly potent therapies to suboptimal therapies, HIV-1 RNA response to therapy may predict clinical endpoint adequately**

# **Surrogate Endpoint Development** **in HIV / AIDS**

- **HIV epidemic in 1990's spurred evaluation of the use of surrogate endpoints, but no surrogate EP has been found to be satisfactory yet**
- **Rigorous statistical criteria for assessing correlation of candidate surrogate with clinical outcome, however, there is no “gold standard” clinical outcome measurement**
- **Survival: data show that desirability of longer survival is dependent on quality of life,**
- **Generalizability of any single outcome measure can be limited by trial parameters**

# **Surrogate Endpoint Development:** **Where is the science progressing?**

- Composite outcome measurements
- Responder rather than population based analyses being considered because drugs work well at individual level rather than on a population level:  
Individual based surrogates

Thank you.