Salvage Studies 4.0

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Presentation Outline

- History of Current Approach to HIV Drug Approval Using HIV-RNA as an Endpoint
- Issues with Current Approach
- Proposal for New Approach
- Potential Benefits of New Approach

Background

- Replication of HIV is in the causal chain of HIV pathogenesis.
- Magnitude and duration of HIV-RNA changes and clinical benefit explored (1996)
- Reductions in HIV RNA predict clinical benefit
- Viral load endpoints used for accelerated and eventually traditional approval

Accelerated Approval

- "Accelerated" a Misnomer—not "fast" approval
- Approval based on Surrogate Endpoint
- ONLY for serious or life threatening illnesses
- ONLY for drugs that provide meaningful therapeutic benefit over existing options
  - "ability to treat patients unresponsive to
  - or intolerant of available therapy,
  - or improved patient response over available therapy."

After Accelerated Approval, the applicant must:

- "Verify and describe the drug's clinical benefit…"
  - "Where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit."
- Prior to 1997, Clinical Endpoint studies required after accelerated approval
  - Endpoint = CDC criteria for an AIDS defining Event (20) and death
- After 1997, HIV-RNA considered validated endpoint

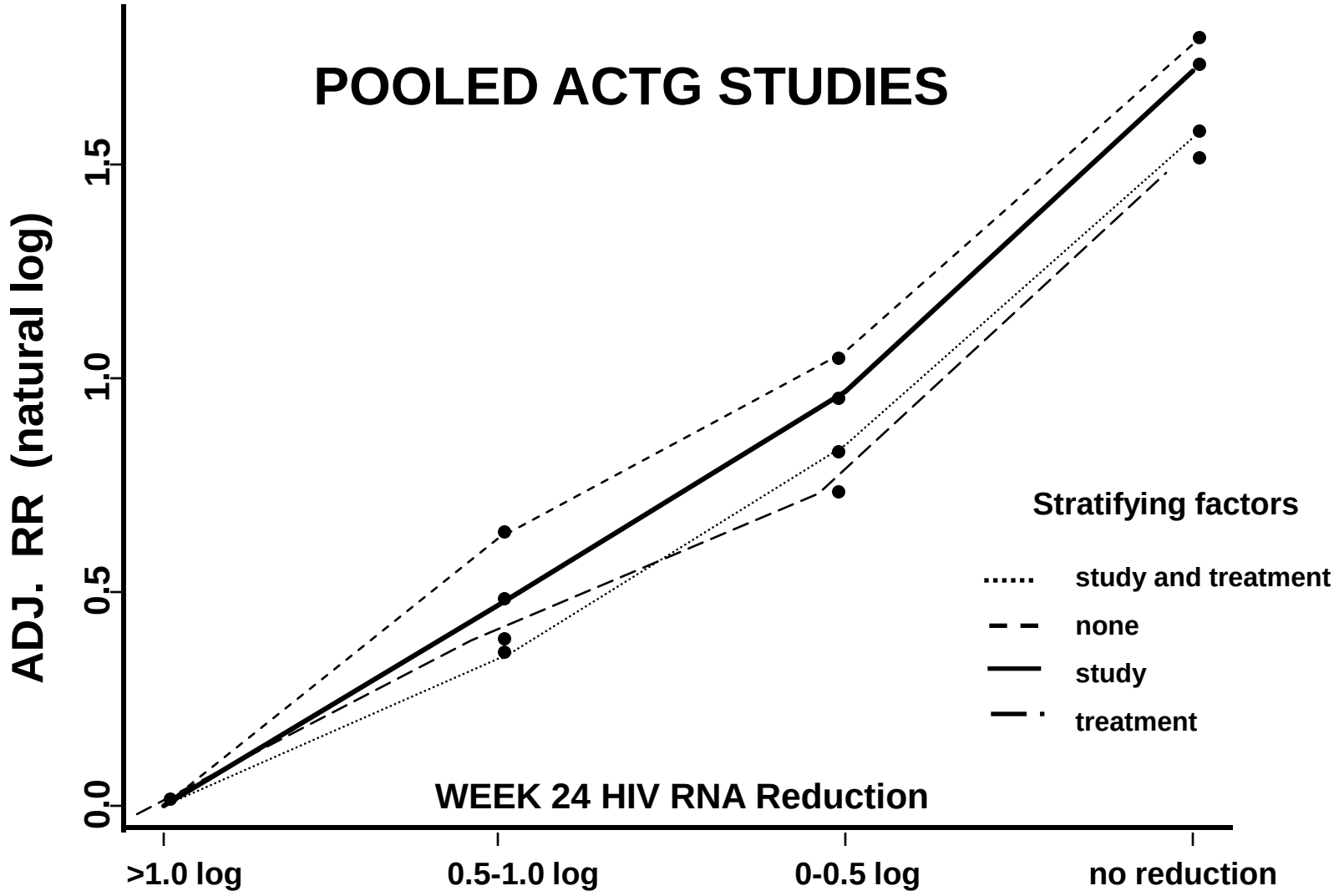
Difficulties with Conducting Clinical Endpoint Studies after 1996

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

Association of Viral Load Reduction and Clinical Benefit

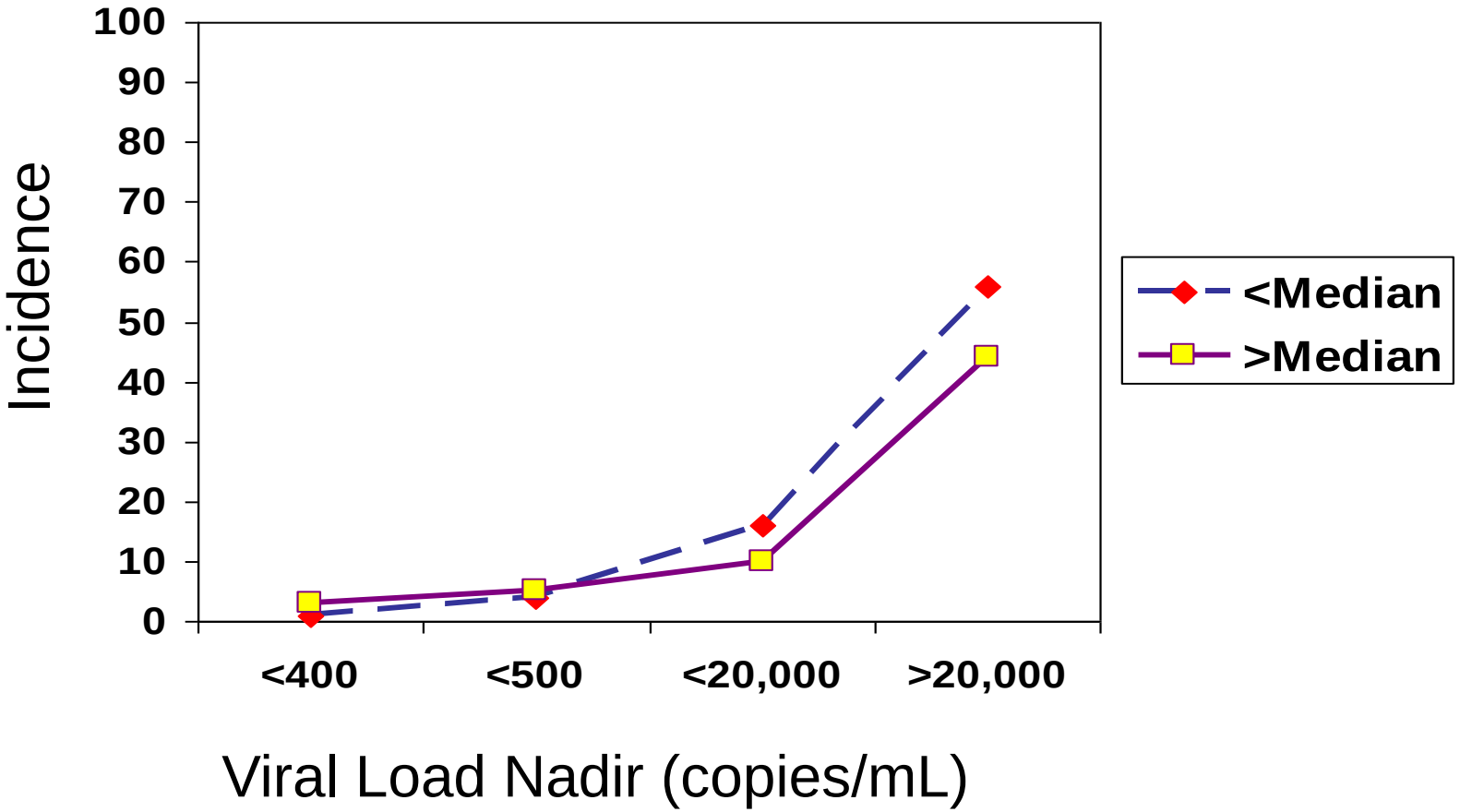
- Magnitude of Reduction
- Nadir of Reduction
- Duration of Reduction

Clinical Progression vs. HIV RNA Reduction



Progression vs. Viral Load Nadir

GSK Analyses



Clinical Hazard by Duration of Reduction

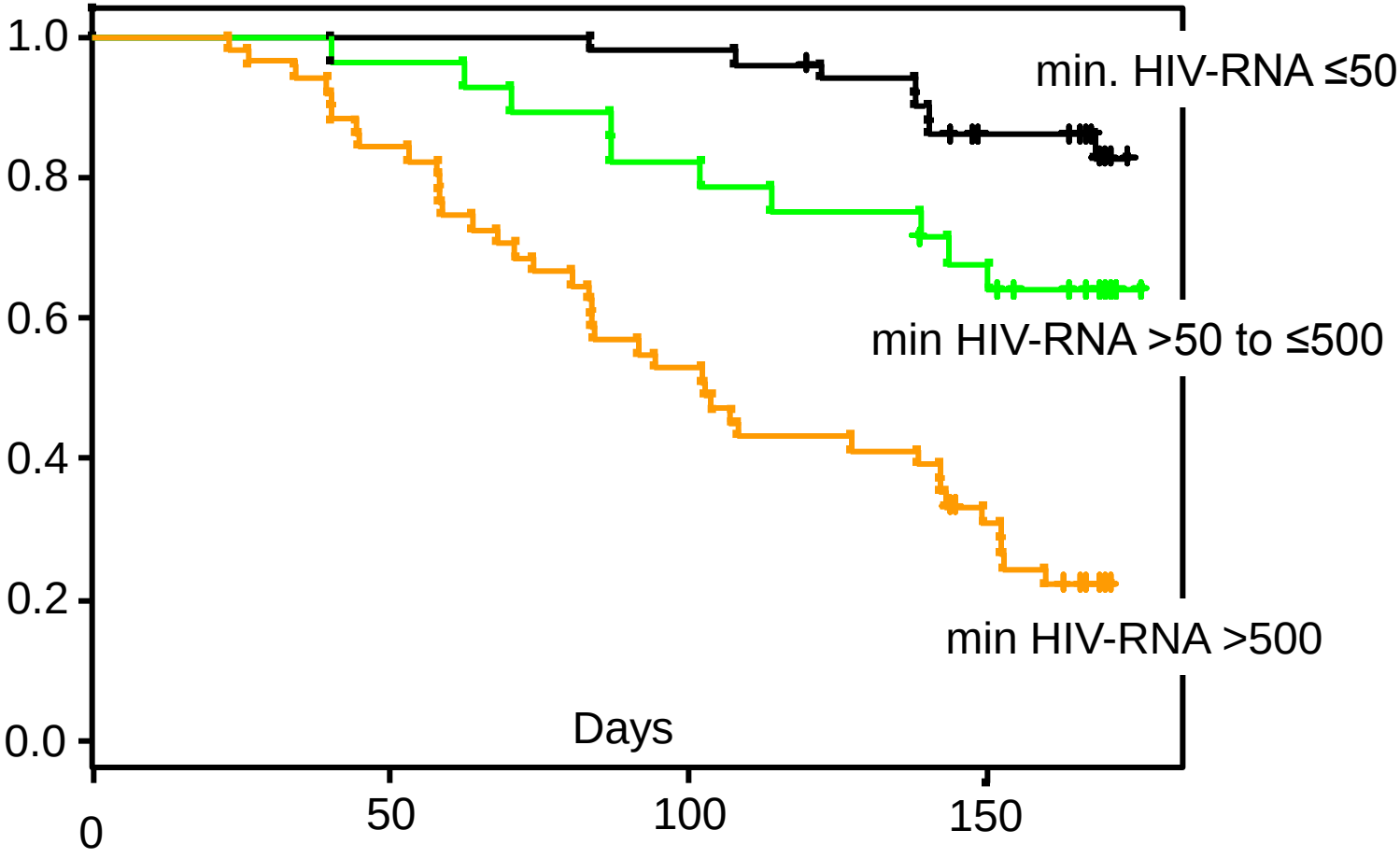
Pharmacia-Upjohn Analyses

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)

Viral Load Reductions and Clinical Hazard

- Previous slides showed correlations using regimens that were not fully suppressive by today's standards.
- Showed that even incomplete or nonsustained responses were associated with clinical benefit (albeit time-limited)
- In 1996—triple drug HAART also entered the scene and the focus turned to a fully suppressive regimen and not just viral load reductions of a single drug or an incomplete regimen

Duration of HIV-RNA Suppression by lowest HIV-RNA Achieved



Drusano et al. JID 1998

Indinavir Regimens

Past (Current) Approach

- Accelerated approval: In a population in need of options (treatment experienced) 24 week HIV-RNA suppression < 50 copies
- Trials: add on to OBR vs OBR
- Traditional approval: 48 week data from continuation of above studies or in another population (compared to an active control in naive)

Accelerated Approval Track Record for current paradigm (since 1996)

- Number of new drugs that received accelerated approval on 24 week viral load endpoints: 13
- Number of drugs that did not retain sufficient virologic effect at 48 weeks: ZERO!
- All accelerated approvals received a traditional approval
- Two drugs (Atazanavir and emtricitabine) had 48 week data in naive patients at marketing and received traditional approval.

In 2010
Are We Facing Another HIV Drug Development Wall?

What are the Trial Design Barriers?

- Superiority Trials: patients are randomized to new drug or placebo (added to Optimized Background)—

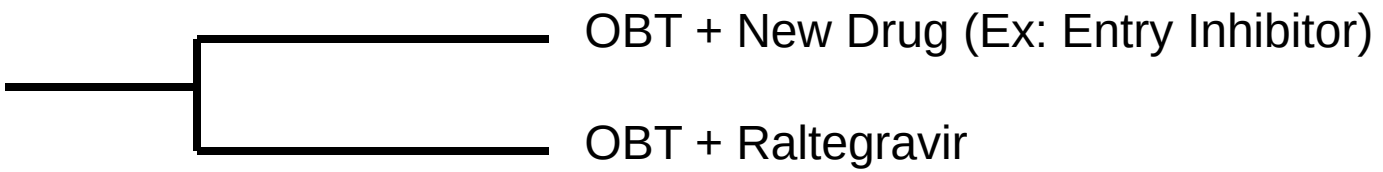
- No longer considered ethical/feasible. Risks resistance to remaining OBT and jeopardizes future options. AND Patients bail from the protocol if they don't have an initial decline. I think people believe that the virologic response in the initial 2-4 weeks tells them the drug is active/efficacious

Q. But what if everyone had at least 2 drugs in their OBT?

A. Runs the risk of not showing superiority (Vicriviroc example)

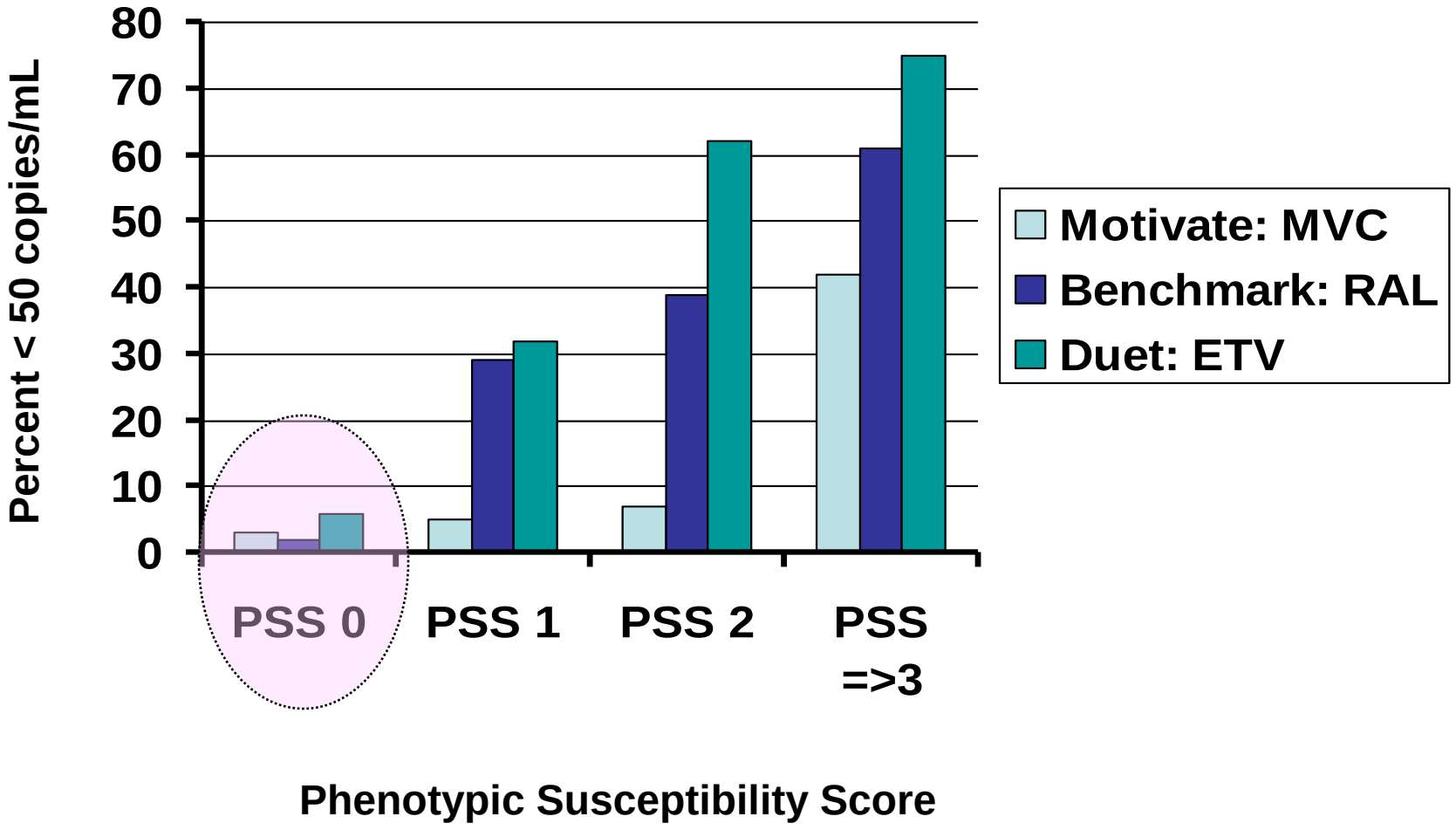
What are the Trial Design Barriers?

- Noninferiority trials: patients are randomized to new drug vs another active drug



- Defining noninferiority margin difficult
  - changing availability of background drugs (does OBT differ from that used in raltegravir trials?)
  - comparability of trials to establish margin (were patients similar)
  - many will want to use raltegravir as part of their OBT or will have already taken raltegravir
- Margin constructed to show that the drug has an effect better than placebo based on previous study of raltegravir compared to placebo
- Margins often only feasible (10-12% range) when majority of patients have GSS/PSS scores of 0 or 1.---Difficult to enroll

Virologic Response (HIV-RNA < 50) for OBT over Trials/Time



Non-inferiority Trials Summary

- Main problem: Defining the non-inferiority margin so that we can determine statistically that the new drug is better than placebo
- But... when we know a drug yields robust viral load decreases in the first two weeks of therapy...
  - Do we really need to be concerned that this drug is no better than a placebo?
  - Is there a risk that we would approve a drug no better than placebo?

In 1996, When We reached a Drug Development Barrier....

We Jumped the Barrier with a New Pathway. In 2010, is it time to develop a new pathway?

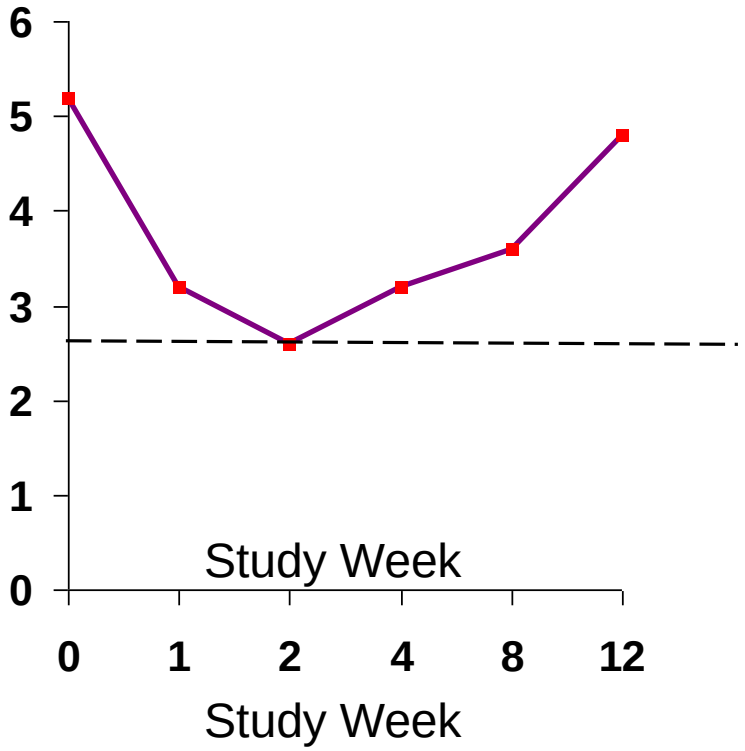
Questions

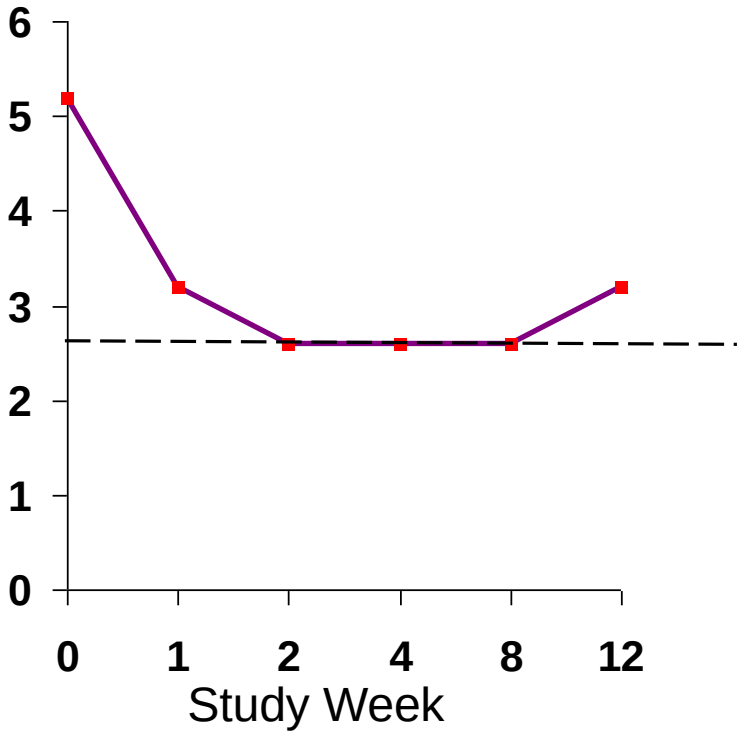
- Isn’t HIV-RNA already a validated endpoint?
- Do drugs with robust early viral load changes lose activity over time when supported with an active regimen?
- Isn’t durability of viral suppression a function of the entire regimen?
- At what time point/duration should an efficacy determination be made?
- Can short term virologic changes establish contribution toward efficacy in populations that are difficult to study

Isn’t HIV-RNA a Validated Endpoint?

- Yes.
- There is no other surrogate marker in drug development that has had as rigorous confirmation or as many confirmatory studies and supportive evidence as HIV-RNA for predicting clinical benefit.

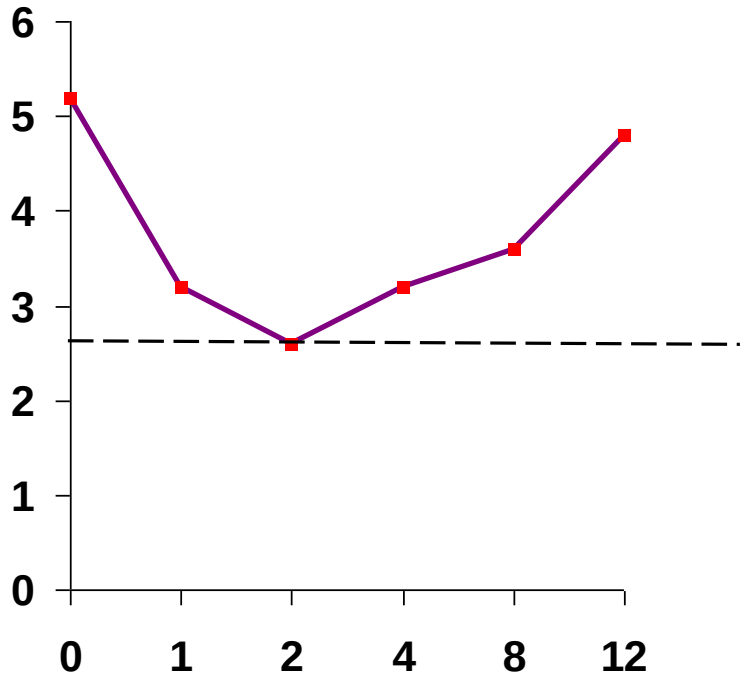
Do drugs with early viral load declines lose their activity when given a supportive regimen?



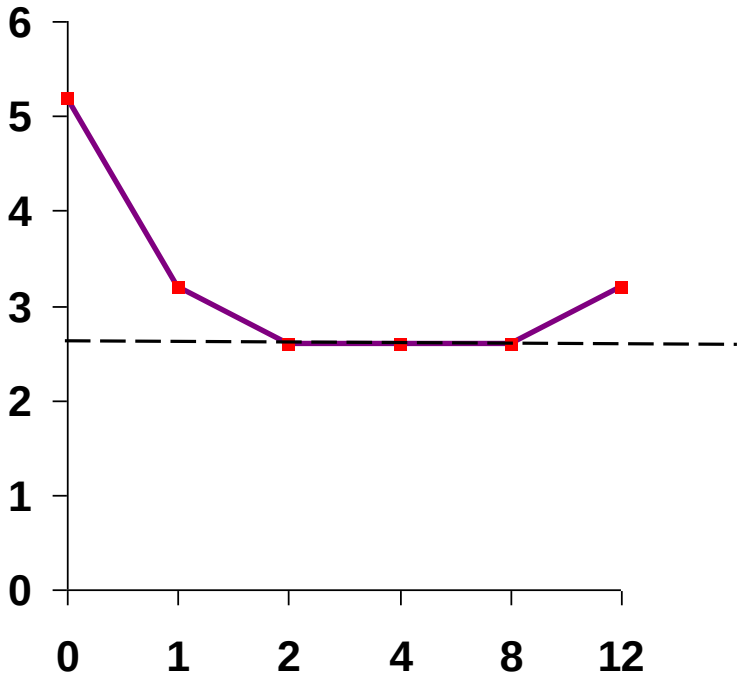


Which drug is more durable? Which drug is more durable in a regimen?

Monotherapy Results
Which Drug is “Better” in Combination?



Efavirenz-like



Kaletra-like

At what time point should efficacy be evaluated?

24 weeks or (less!)

48 weeks (or more?)

fewer options

superiority trials

no standard regimens

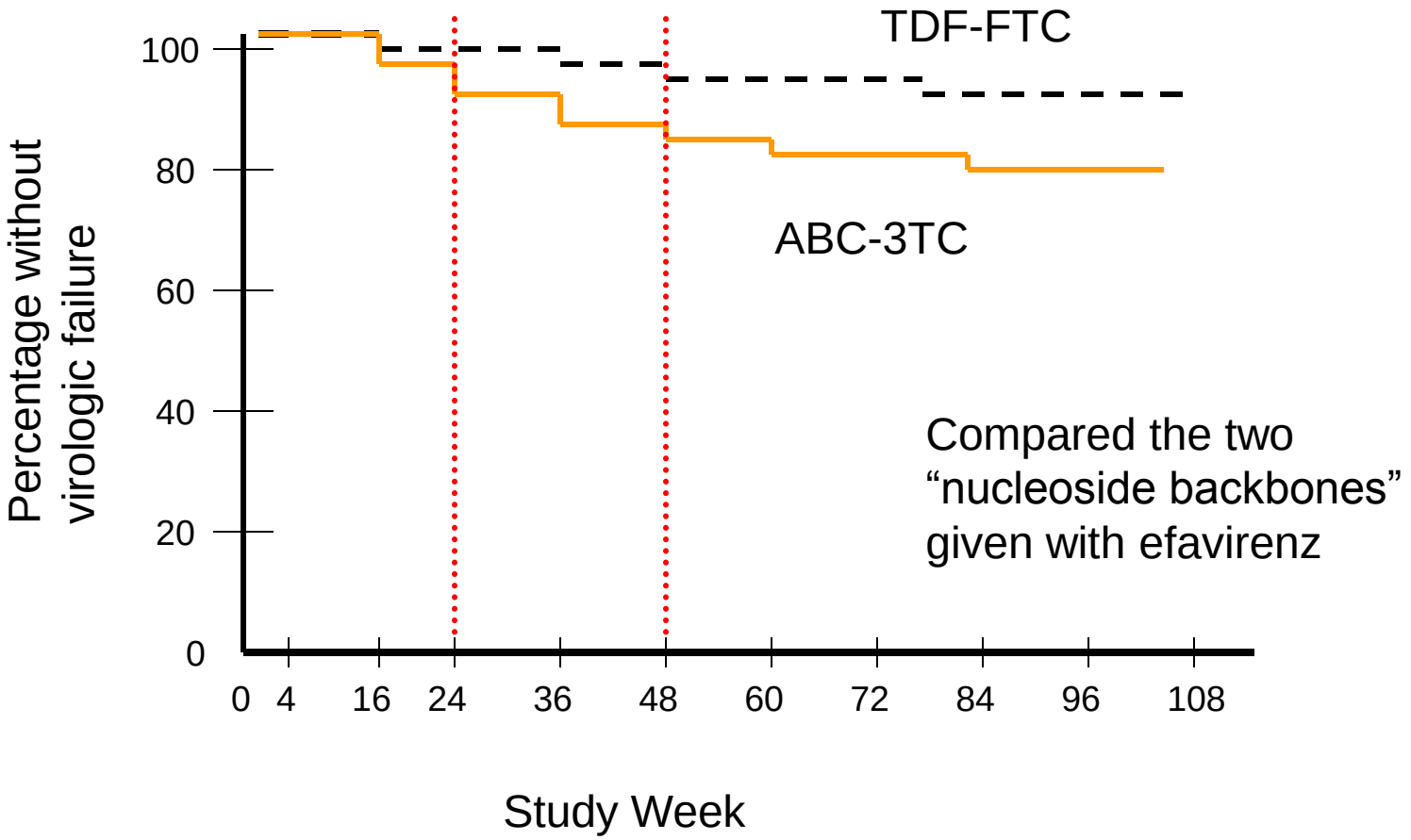
many options

noninferiority trials

standard regimens

Naive Patients: ACTG 5202

Patients with >100,000 HIV RNA at Baseline



48 week Endpoint Evaluation most appropriate for

- Comparison of treatments expected to be similar or modestly different
  - noninferiority studies
- Comparisons of drugs used with a standard background regimen in which the treatment effect is well characterized an reproducible
- Treatment Naive or Early Treatment Failures—Desire labeling that describes even modest differences in relative efficacy to help physician sort out most appropriate option when considering multiple potential options.

What do we need to know to consider using a new drug in a population who is at high risk of HIV morbidity and has few remaining options?

- Need to know that the drug is better than placebo (regulatory hurdle)
- Need to know the most active dose
- Information on how to combine it with other drugs (drug interactions/antagonism)
- Safety for 24 weeks

Proposal (part a)

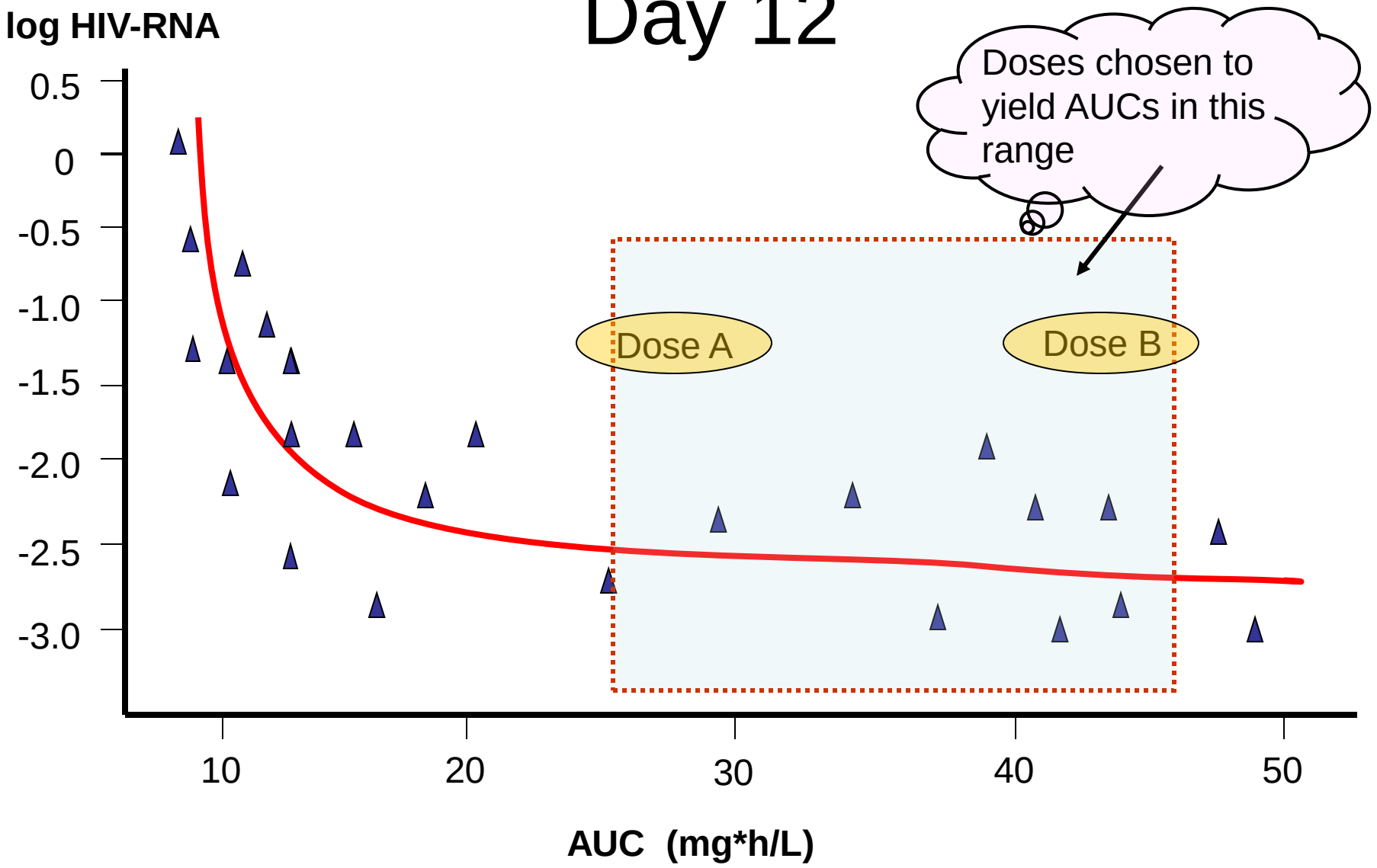
For Highly Treatment Experienced Patient who need a new drug to construct a regimen

- For the types of drugs under #1 and #2
  1. New Drug Class (e.g, entry inhibitors)
  2. Existing Drug Class But Can Treat Virus Resistant to Approved Option(s), e.g., second generation integrase inhibitor
  3. Existing Drug Class with No Advantages Relative to Resistance/Efficacy, e.g., a second integrase inhibitor with resistance profile like raltegravir

Proposal (a): Heavily Treatment Experienced Patients

- Phase 1 studies in healthy volunteers
  - single and multiple dose PK
  - drug-interaction studies
- Phase 1-2 Proof-of Concept
  - initial safety and dose finding in smaller numbers (10-20 per arm)
  - if monotherapy safe, initial functional monotherapy or monotherapy (in naives) for 1-2 weeks followed by continuation in regimen for initial safety

HIV-RNA Changes by AUC Day 12



Dose finding

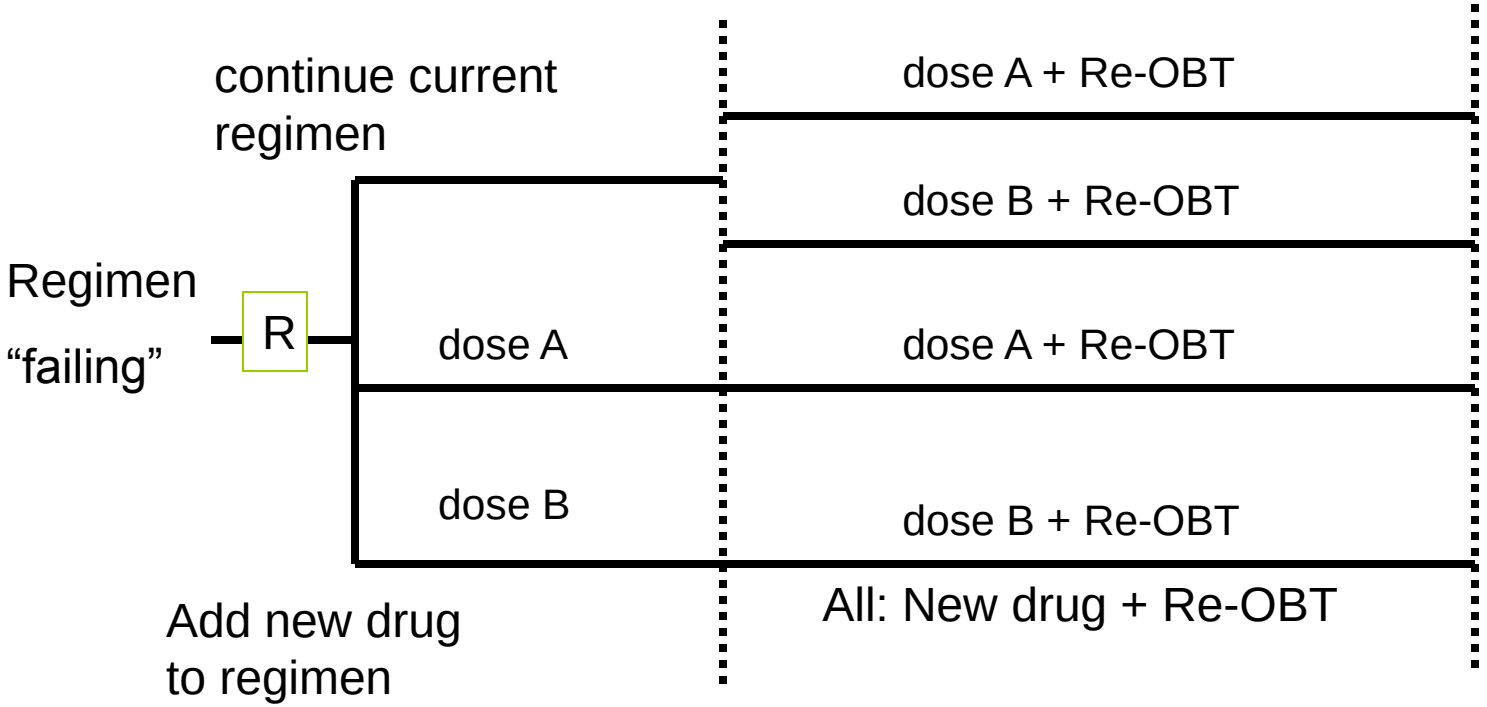
- Initial dose finding: measures first phase of viral decay. May underestimate dose if:
  - Subsequent phases need higher exposures (compartment/tissue concentrations)
  - Or needed to suppress subsequent emergence of existing viral mutant minority strains (pre-existing variants with lower susceptibility).
- Thus, longer term dose confirmation (24 weeks) as part of a regimen optimal.

Proposal (part a)
Highly Treatment Experienced Patients
Phase 3

- 2 week changes in viral load satisfy regulatory hurdle of “better than placebo”
- 24 week evaluation of multiple doses in combination with OBT to evaluate an optimal dose or assess a dose response
- 24 week evaluation of safety as part of a combination
- 24 week evaluation for development of resistance and for assessing virologic response associated with baseline resistance patterns

Proprosal (a) Phase 3 Trial Design

Treatment Experienced: can't construct a viable regimen without a new drug



Primary Efficacy Assessment

Safety Assessment

Dose Comparison

Resistance Assessments

Proposal (part b)

- For Treatment Experienced:
- Drug Comparable to an Approved Drug:
- 24-48 weeks noninferiority comparison to approved drug. Endpoint proportion below LOQ
- Endpoint: viral load changes at earlier time point, if drug previously approved drug based on shorter term virologic changes. Also show comparability of effect at 24 weeks.

Proposal (part C)

- For Naive patients and Early Treatment Experienced: 48 weeks compared to a gold standard regimen—allows for stringent comparison of efficacy. Endpoint: proportion below LOQ

Benefits of New Paradigm

- Open up HIV drug pipeline
- Offer clear pathways to approval
- Quicker enrollment
- More palatable study designs for participants
- Less risk of jeopardizing remaining treatment options for trial participants
- Fulfill the intent of existing regulations—e.g., accelerated approval, for populations in most need of new therapies and when drugs can potentially provide benefit over approved options.