Salvage Therapy II

aka Therapy for Extensively Pre-Treated HIV+ Patients

Summary of the Forum Workshop

Veronica Miller, PhD

7th International Congress on
Drug Therapy in HIV Infection
Glasgow 14-18 November 2004

The Forum for Collaborative HIV Research is a public/private partnership including academia, advocacy, government agencies, foundations, industry.

Our mission is to facilitate and enhance HIV research.

Salvage Therapy II Workshop – April 2004

Co-sponsored with the Houston Center for AIDS Hope and Remembrance Project

Dedicated to L. Joel Martinez 1953-2003

- Follow up to the earlier Forum meeting:
- The Challenges of Clinical Trial Design in Assessing the Effects of Anti-HIV Therapy in Heavily Pre-treated Patients
  - May 1999
  - Followed by FDA Antiviral Advisory Committee Meeting 1/01

Goals: 1999

- To discuss the design and implementation of studies of salvage therapy regimens in heavily pre-treated patients.
- To present needs, priorities, and challenges faced by industry, researchers, regulators and patients.
- To define treatment failure and success.
- To understand and agree what is necessary and feasible when designing studies of new drugs for salvage therapy.

Context: 1999

DHHS Guidelines:

Table XVI: Possible Regimens For Patients Who Have Failed Antiretroviral Therapy: A Work in Progress*

*These alternative regimens have not been proven to be clinically effective….Clinical trials in this area are urgently needed

- Challenges in study design:
  industry, regulatory, virology, clinical, patient
- Statistical issues
- Endpoints
- Pharmacologic issues
- Regulatory and industry issues of multiple therapies in salvage studies

Context: 1999 Industry/Regulatory Issues

- Salvage setting recognized as serious/life threatening
- No accepted standard of care
- Recognition of different risk:benefit ratio
- Investigational agents available through RCT, emergency IND (single patient), treatment IND/parallel track
- Multiple investigational agents OK, but need to assess individual safety/efficacy

Context 2004

- DHHS Guidelines March 2004:

"[The TORO trials] support the strategy of … designing a new regimen based on the treatment history and resistance testing results, and selecting active antiretroviral agents for the new treatment regimen."

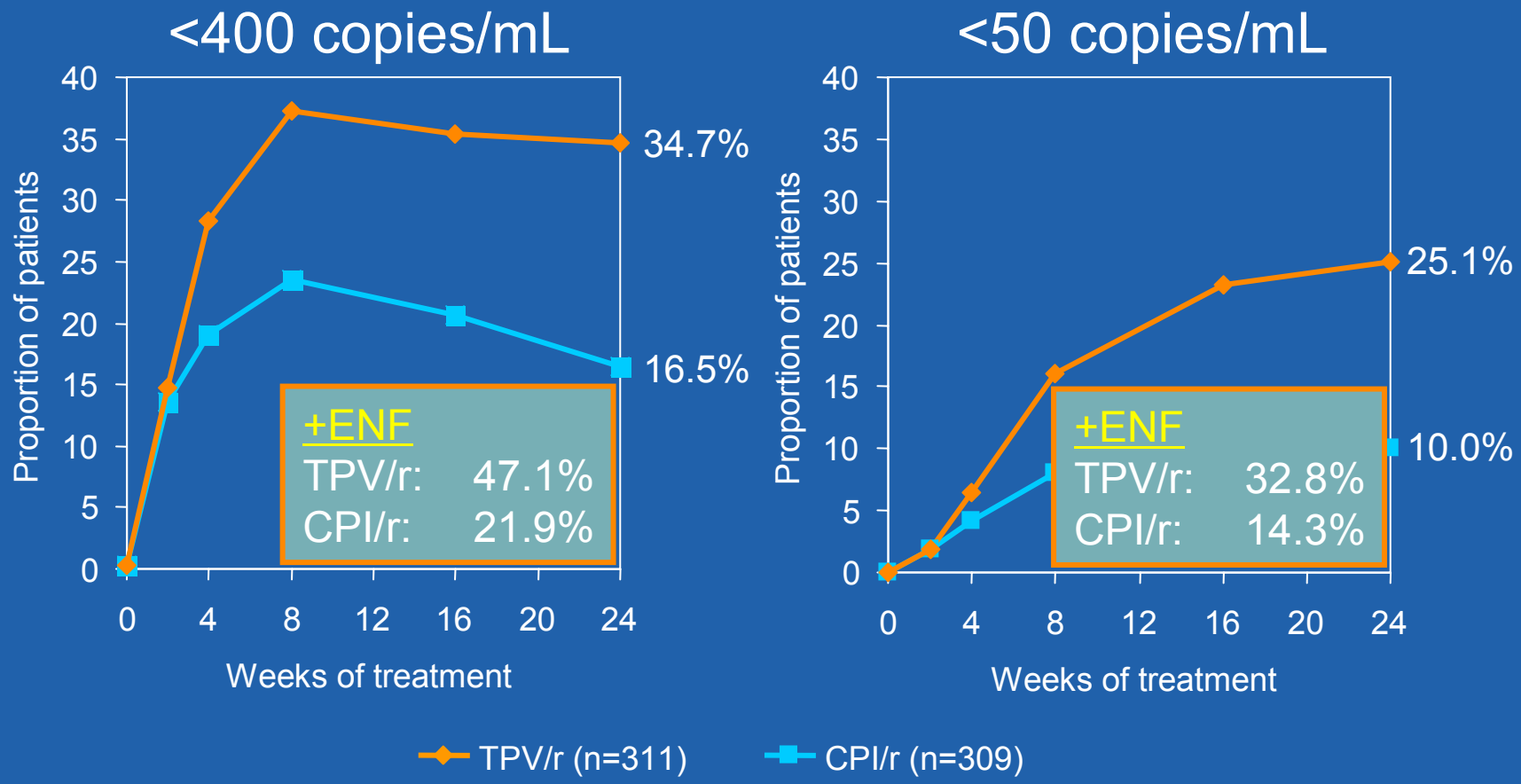
1999 → 2004

- 14 (3) → 20 (4)
  - More drugs but also more treatment experience
- Resistance testing as standard of care
- Therapeutic drug monitoring (Europe >> US)
- "2nd generation" agents
- Other entry inhibitors in clinical trials
- Treatment strategies investigated
  - Intensification
  - STI/PTI
  - Mega/Giga-HAART

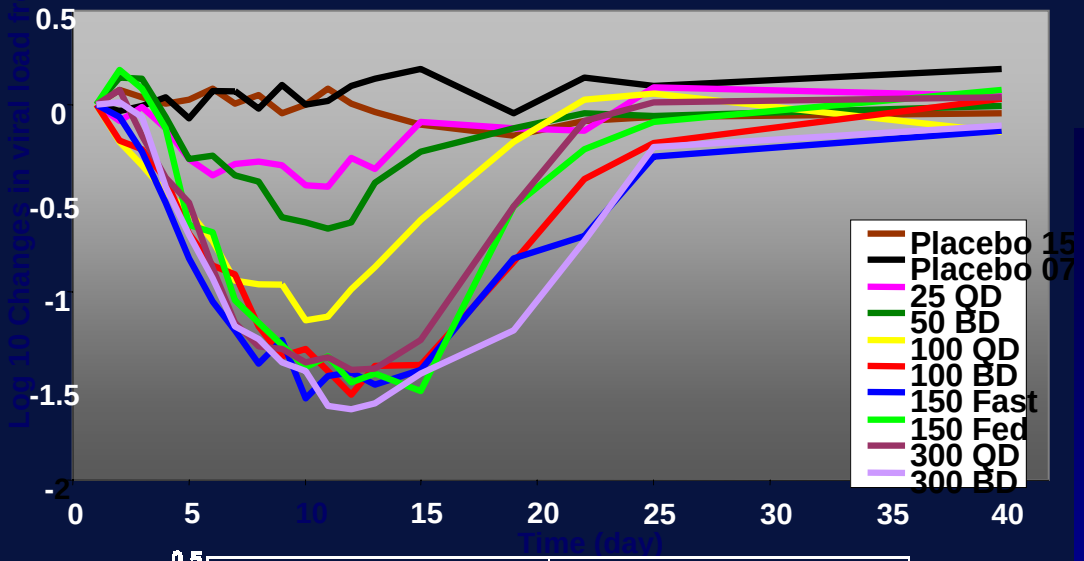
RESIST-1

Proportion with undetectable viral load

Intent-to-treat: non-completer = failure



Pfizer K 427 857



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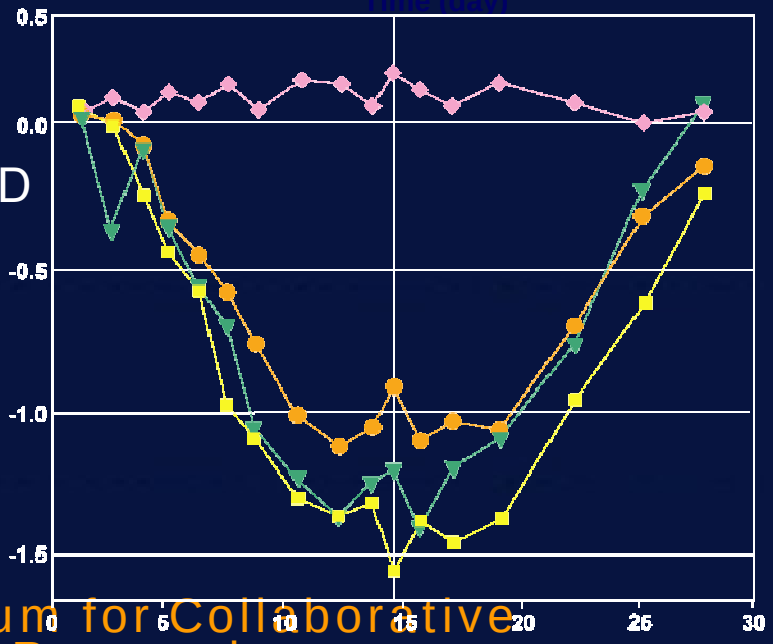
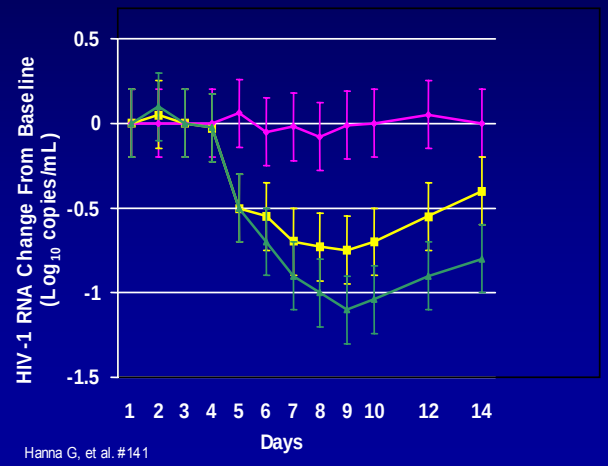


BMS-488043, a novel attachment inhibitor

- Phase 1b dose-ranging study, 30 treatment-naive pts



Hanna G, et al. #141

Forum for Collaborative HIV Research
www.hivforum.org

Miller November 2004

School of Public Health & Health Services

The George Washington University

Current “salvage” research

- Optimized background regimen
  - Resistance testing
- Allow drugs available through expanded access programs to be included in optimized background
- Allow 2:1 randomization
- Cross-over to new drug arm
  - Problem with diminishing control arm

2004: Unmet Needs

NRTIs	Activity against resistant strains Lower drug toxicities
NNRTIs	Activity against resistant strains
PIs	Activity against resistant strains Increase drug levels without increasing toxicity Reduce pill count and dosing frequency
Entry Inhibitors	Oral bioavailability Cost
Rx Regimen	Simple & tolerated Co-formulation Studies in women and racial/ethnic groups Studies in non-clade B settings

HIV+ individual perspective

- "How do you gauge success?"
  - Quality of life, stability, low viral load, healthy amount of T cells
  - Survival
  - May have been defined as "treatment failure" within RCT setting
- Allow >1 new drug to be combined
  - Maybe willing to take risks
  - Advocate for more industry collaboration
- Earlier expanded access programs
- Greater flexibility for individual patient needs

Combining more than one experimental drug

- >1 drug in RCT
  - Coincidence vs intent
  - Assignment of toxicity & efficacy
- Allow use of expanded access drugs in OBR
  - Balance against risk of competing for enrolment in RCTs
  - If no enrolment in RCTs: delay in approval of drugs for all eligible patients

Regulatory perspective: Balance access with need to obtain scientific data

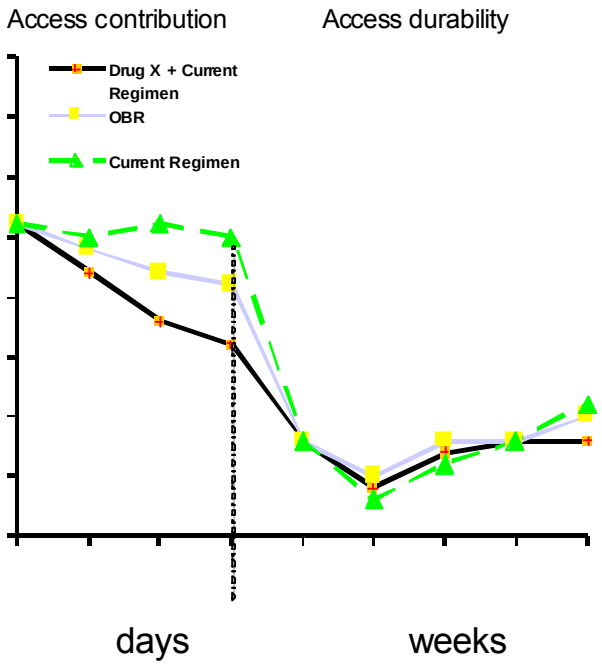
- Accelerated approval if indication for treatment experienced patients, drug resistant virus
- Risk/benefit for Rx naïve patients also changing!
- Safety & efficacy adequately investigated
- Clinical Trial designs:
  - Traditional design: OBR + ND; OBR + placebo
  - Modified factorial: PK, dosing, industry collaboration required
  - Two-part hybrid: new drug vs placebo for 2 weeks followed by everyone receiving new drug
  - Open label, non-comparator “compassionate use”

Study Design Options

A: Modified Factorial Design

- Four arm trial for 3 investigational agents (Drugs A, B, and C)
  - OBR + A + B
  - OBR + A + C
  - OBR + B +C
  - OBR + A + B + C
- Assumption is that OBR or OBR + single study drug alone is inferior
- N is 33% less than needed for 3 separate trials

B: Two-Part Hybrid Design



Industry perspective

- Challenges in development:
  - Heterogeneity of patient population
    - Plus and minus
  - Heterogeneity of virus population (for CCR5 inhibitors)
  - Identification of acceptable comparator arm
    - Blinding frequently not possible
  - Identification of achievable and clinically relevant endpoints
  - Complex efficacy and safety evaluation due to cross-over options
  - Development of new tools (e.g. R5/R4 virus typing)

Clinical Management Perspective

- How to switch:
  - Wait for more than one drug or risk use of one new drug?
- Safety & efficacy:
  - Pharmacokinetic interactions, sometimes unexpected

Research perspective

- What is the role of:
  - Viral fitness/loss of fitness
  - T cell activation/ suppression of activation?
- Where is the “salvage population” going?
  - Current Rx experienced patients: AZT mono, 2x combination, etc
  - Patients starting Rx on current standard-of-care?
  - How will we assess the “salvage needs” for the future?

Discussion & Recommendations

- Development of effective strategies for the management of HIV-infected antiretroviral treatment-experienced patients is a public health priority.
- Challenges in the design and conduct of trials in treatment-experienced patients remain
- Collaboration between pharmaceutical companies, clinicians, clinical researchers, the HIV-infected community and government agencies are paramount for the successful development of new therapies and effective treatment strategies

Discussion & Recommendations

- Maximize opportunity to study multiple new drug combinations
- More systematic use of cohort data & expanded access programs
  - E.g. French ATU model
- Facilitate easier handling of expanded access and compassionate use programs
  - Less burdensome for clinical research centers
  - Competing with need to engage in “funded” research
- Support mechanisms to determine extent of “salvage” need
- Use of research networks for proof-of-concept studies

Special Thanks

- Presenters
  - –Trip Gulick, Miklos Salgo, Joel Gallant, Richard Ogden, Steve Deeks
- All panelists & workshop participants
- Steering Committee
  - –Roberto Arduino, Ben Cheng, Cal Cohen, Steve Deeks, Tom Gegeny, Gregg Gonsalves, Trip Gulick, Dorothy Lewis, Veronica Miller, Jeff Murray, Lynn Smiley, Kim Struble

Salvage II Think Tank Funders

Baylor–UT Center for AIDS Research (CFAR) (local planning partner)

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