Salvage Therapy Today

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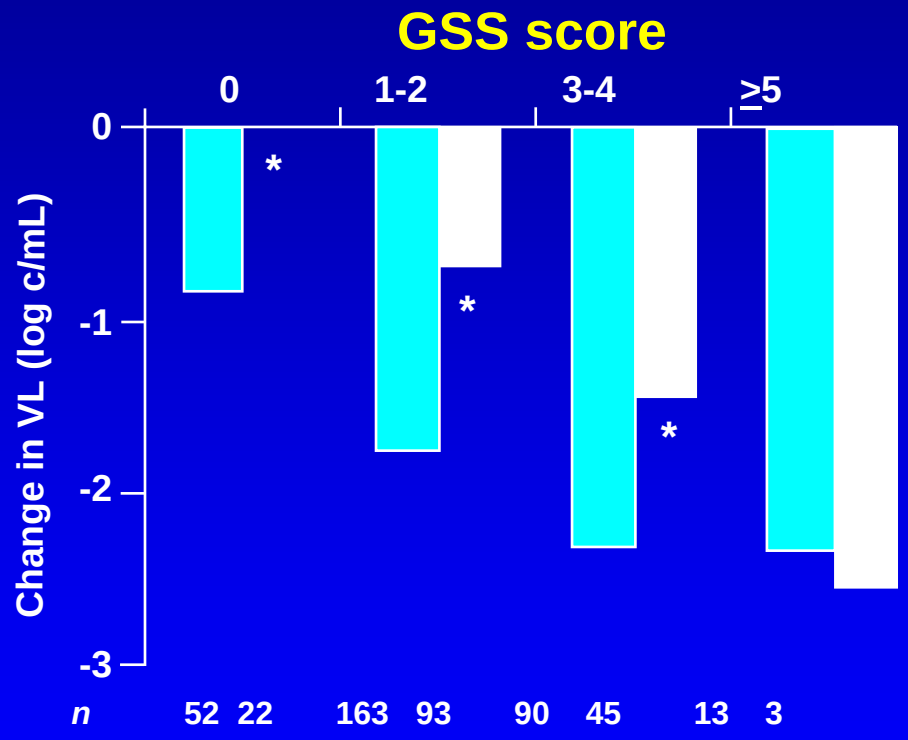
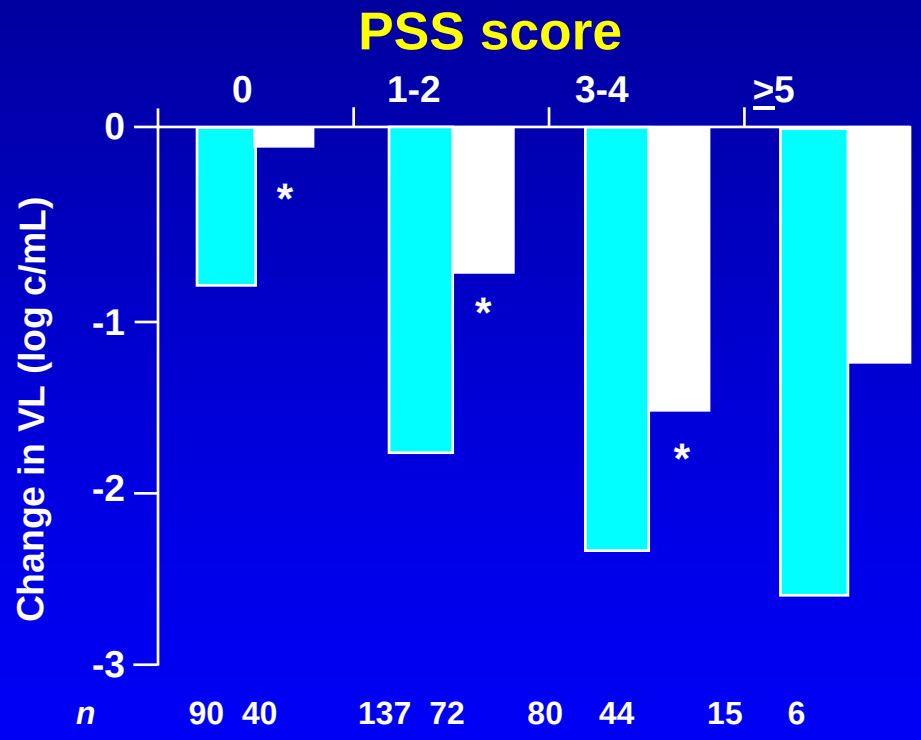
- Examples of recommended sequences:
  - 2 NRTIs + PI→2 new NRTIs + 2 PIs *or* 2 new NRTIs + NNRTI/PI
  - 2 NRTIs + NNRTI→ 2 new NRTIs + PI
- No mention of resistance testing

DHHS Guidelines: March 23, 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."

Enfuvirtide (T-20): TORO 1
Virologic response by level of resistance





Least squared means log change from BL (LOCF) – ITT population

ENF + OB

OB

*$p<0.05$

Lalezari J, et al. 42nd ICAAC, San Diego 2002, #H-1074

New Developments in Salvage Therapy since 1999

- Therapeutic drug monitoring
- Intensification
- STI
- PTI
- Mega-HAART
- "2nd generation" agents
- Approval of 4th class (fusion inhibitor)
- Other entry inhibitors in clinical trials
- Many early "salvage trials" were not salvage trials by today's definition: (e.g. NNRTI-naïve)
- Resistance testing as standard of care

Intensification

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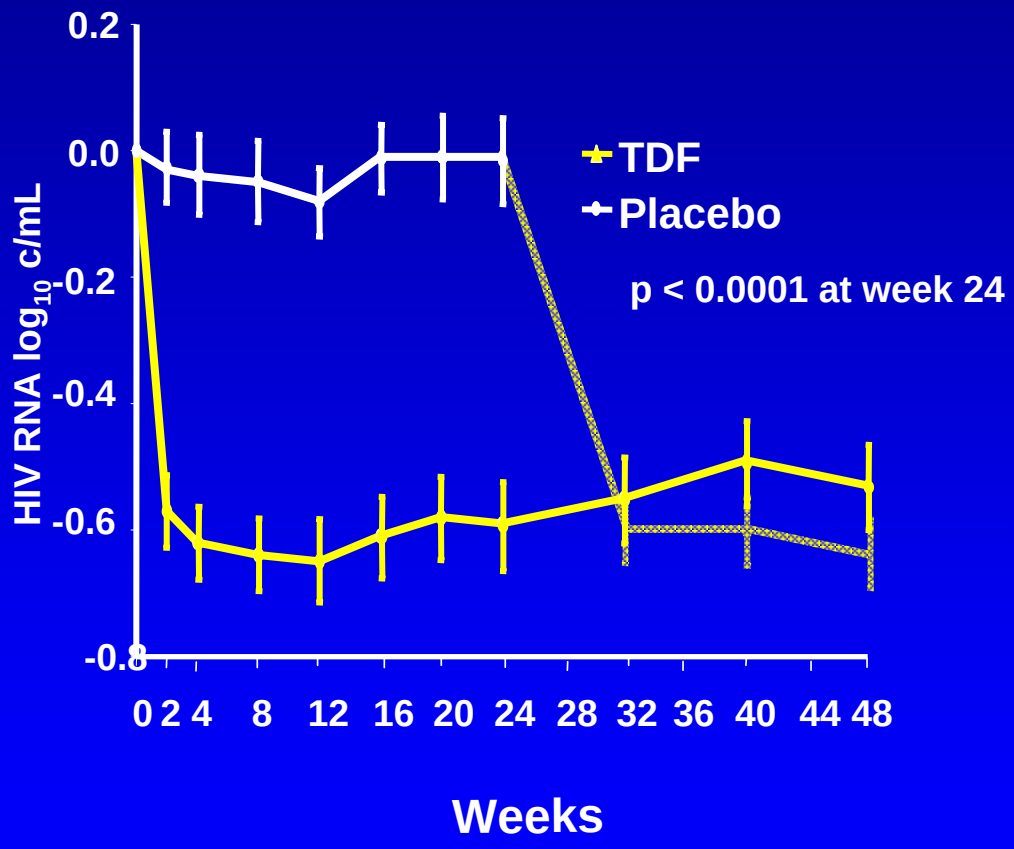
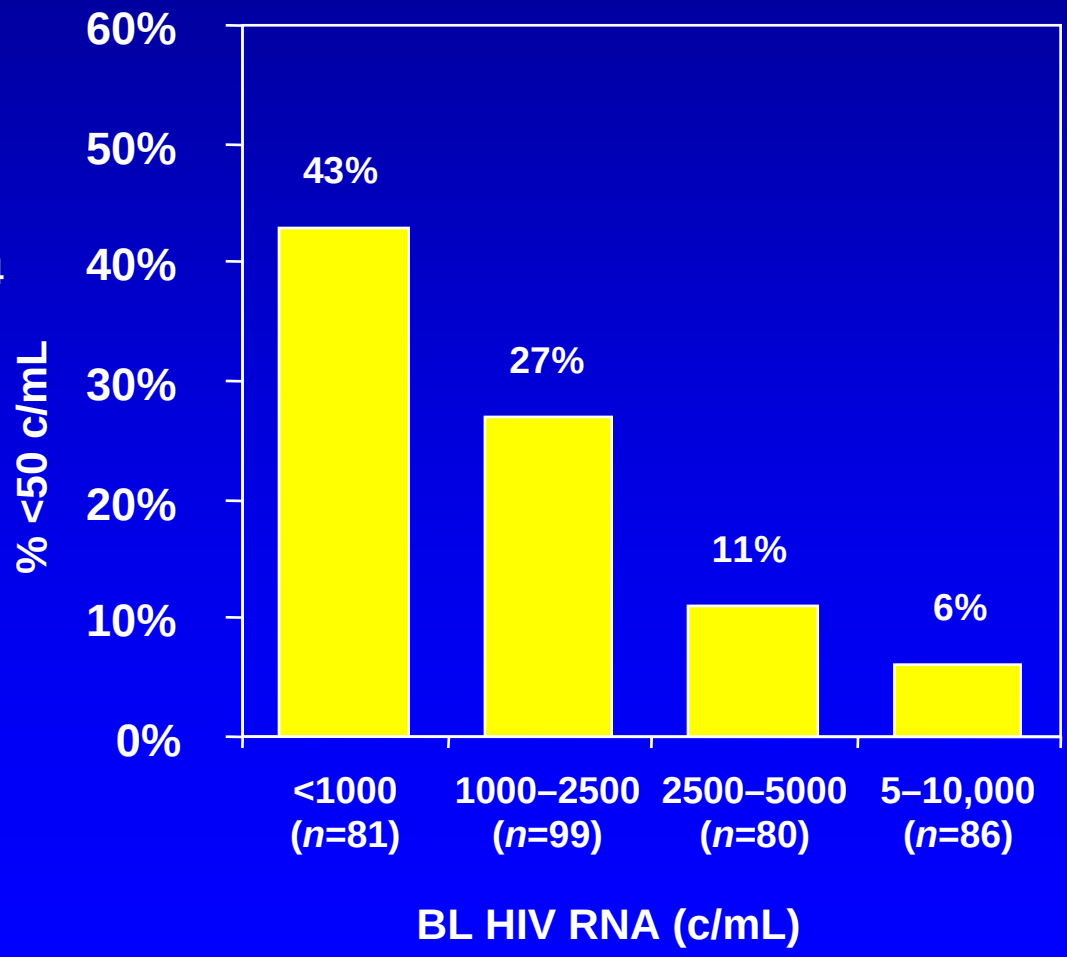
Examples:

-Virologic intensification: addition of ABC, TDF, ddI

-Pharmacokinetic intensification: addition of RTV boosting

Tenofovir vs Placebo:
Intensification of Failing Regimen (GS 907)





Squires K *et al*. 9th CROI, Seattle, 2002, #413

Intensification Studies

PROs

- Easy to enroll
- Assesses efficacy of drug in experienced patients
- Assesses activity across range of resistance (determine clinical cut-off)
- Collects data on a variety of combinations

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CONs

- Inappropriate strategy for most new agents based on resistance concerns
- Minimal support for intensification except at low viral loads (e.g. <1000 c/mL)
- Efficacy at low viral loads does not assess true potency

Use of Resistance Testing

Randomized Controlled Trials of Resistance Testing in the Setting of Virologic Failure

Study	Design	1st PI Failure	ΔRNA (log_{10})	% RNA<400
GART[1]	G vs SOC	~40%	-1.04 v-0.46	29 v 14
Viradapt[1]	G vs SOC	~50%	-1.19 v-0.61	34 v 22
VIRA3001[1]	P vs SOC	100%	-1.72 v-1.21	46 v 34
Kaiser[1]	P vs SOC	25%	-0.2 v-0	NA
NARVAL[1]	P vs G vs SOC	<30%	-1.0 v-1.1 v-0	35 v 44 v 36
HAVANNA[1]	G vs SOC	10%	-1.3 v-1.1	66 v 53
ARGENTA[2]	G vs SOC	NA	-0.57 v-0.39	NA
CCTG 575[3]	P vs SOC	>90%	-0.73 v-0.69	48 v 48
Realvirfen[4]	Real P vs virtual P	NA	-0.9 v-1.3	NA

- **Using either genotypic or phenotypic testing resulted in delayed time to persistent virologic failure in treatment-experienced patients in a long-term study of the efficacy of resistance testing (CERT).[5]**

G=genotype; SOC=standard of care; P=phenotype.

1. Demeter L. 7th CROI; Jan 30-Feb 3, 2000; San Francisco, Calif. Abstract S32. 2. Cingolani A, et al. *AIDS*. 2002;16:369-379. 3. Haubrich R, et al. *Antivir Ther.* 2001;6(suppl 1):63. 4. Wegner S, et al. *Antivir Ther*. 2002;7:S129. Abstract 158. 5. Perez-Elias MJ, et al. *Antivir Ther.* 2002;7:S89. Abstract 109.

When to Use Resistance Testing: Summary of Guidelines

	IAS-USA	DHHS	EuroGuidelines Group
Primary naive	Recommend	Consider	Recommend
PEP	—	—	Recommend
Chronic naive	Recommend if ≤ 2 yrs	If >5% prevalence	—
Failure	**Recommend**	**Recommend**	**Recommend**
Pregnancy	Recommend*	—	Recommend*
Pediatric	—	—	Recommend†

*Only if mother viremic
†Only if mother was viremic and on treatment at time of birth.

Which Resistance Test?

- Evidence supports use of resistance testing with virologic failure
- Few trials compare one technology with another; so far the data are inconclusive
- Preferences for one test over another are often driven by non-data driven considerations

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- Genotype
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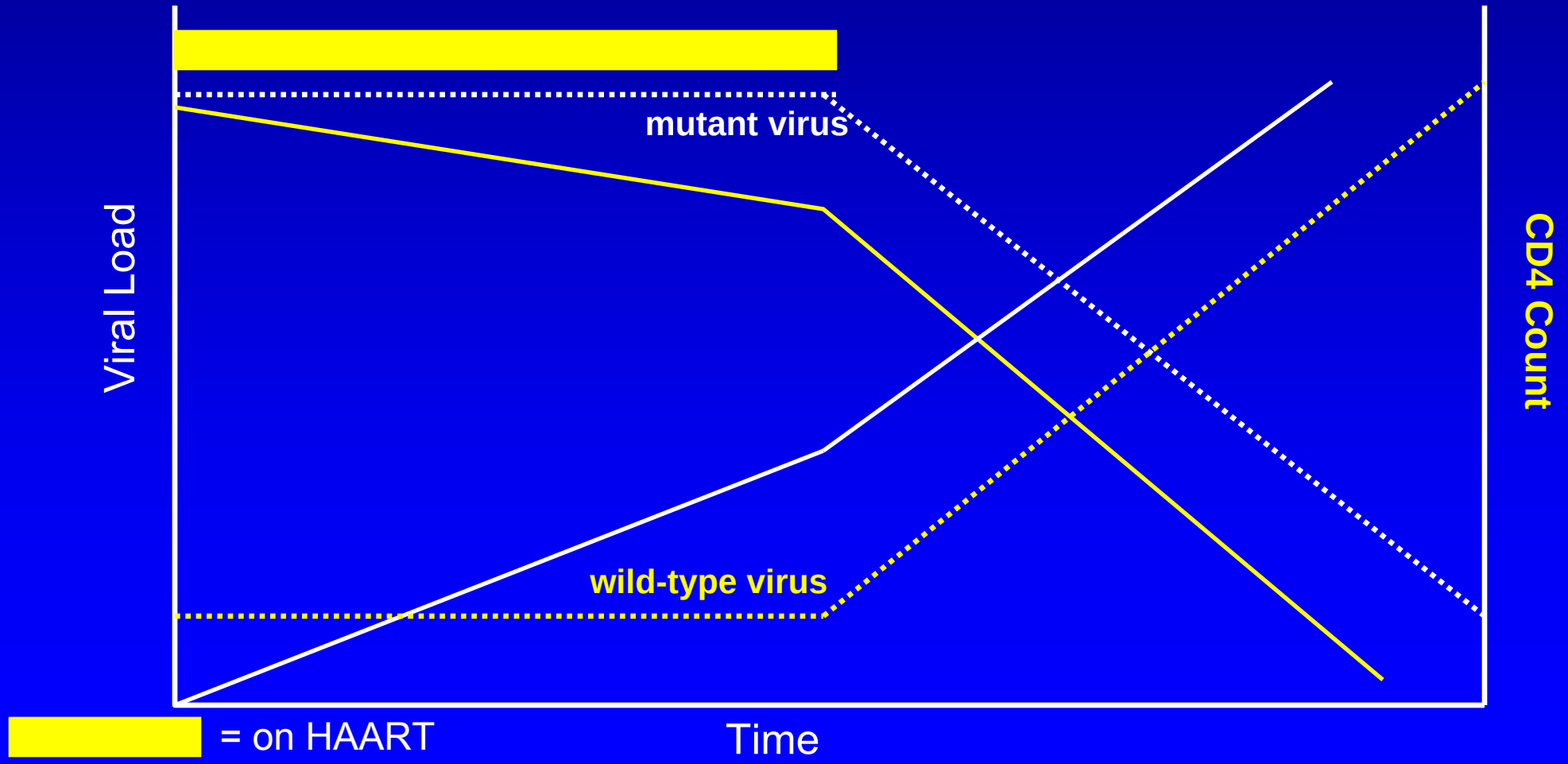
- Genotype + Phenotype
  - What to do about discordance?
  - Mixtures vs. non-mixtures

Approaches to the Treatment of Highly Resistant Patients

“Dual Boosted PIs”

- Usually a combination of LPV/r plus PI, e.g.:
  - LPV/r 400/100 + SQV 1000 bid
  - LPV/r 533/133 + APV 750 bid
- Choice based on resistance, tolerability, PK data
- Minimal clinical data: regimens usually chosen because of lack of adequate NRTI or NNRTI options
- Current regimens are difficult:
  - 500 mg *Invirase* formulation will simplify LPV/r + SQV combination
  - Unclear whether FPV can replace APV when combined with LPV/r
  - No data on ATV

Virologic/Immunologic Discordance
The Effect of Mutant vs. Wild-Type Virus



Treatment Interruption prior to Salvage Therapy in Highly Resistant Patients

- GIGHAART[1] (n=70): improved virologic control with 6-8 drug salvage regimen after 8-week interruption compared to immediate salvage (-1.9 log vs. -0.4 log, p=0.008)
  - » Minimal reversion of resistance mutations

1. Katlama C, *et al*. *10th CROI*, Boston, 2003, #68

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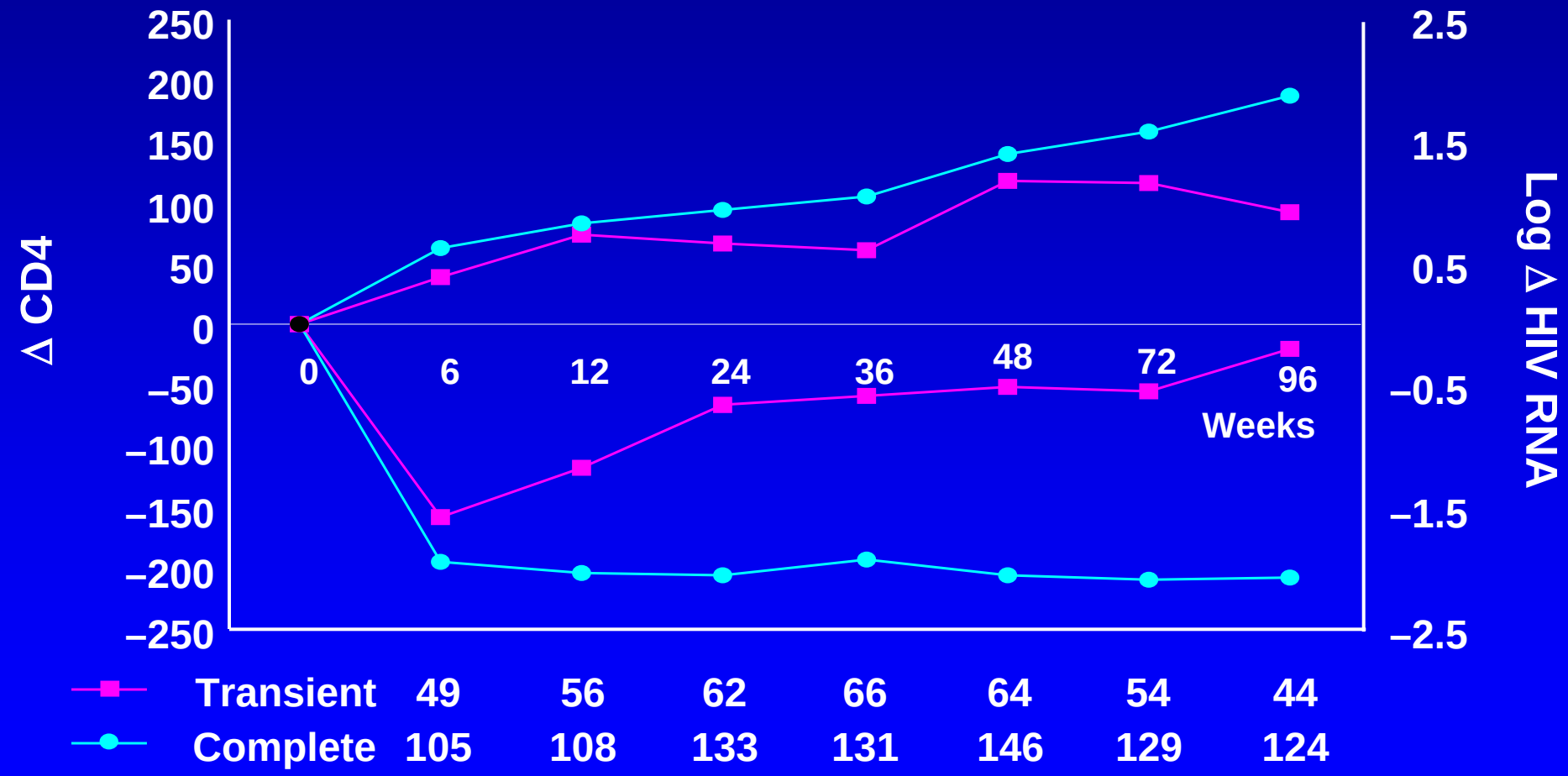
- CPCRA 064[2] (n=245): no benefit to 16-week interruption before 4-drug salvage therapy
  - » More clinical events with interruption (22 vs. 12, p=0.01)
  - » CD4 remained lower in interruption arm at 20 months
  - » Significant reversion of resistance mutations

1. Katlama C, *et al*. *10th CROI*, Boston, 2003, #68
2. Lawrence J, *et al*. *10th CROI*, Boston, 2003, #67

Treatment Interruption prior to Salvage Therapy in Highly Resistant Patients

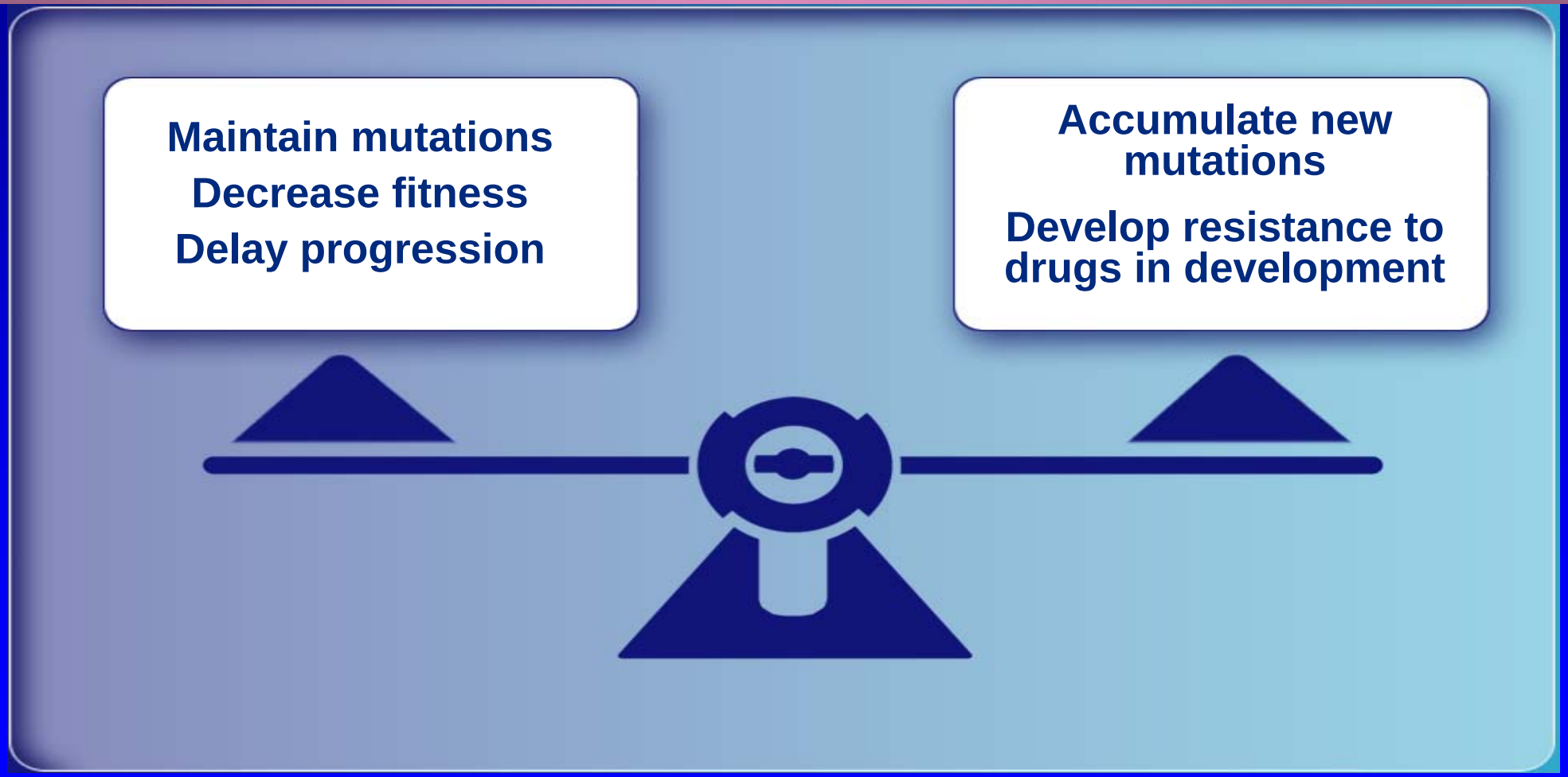
- The relevance of reversion & the length of interruption
- “Mega-HAART” vs. standard salvage
- The role of adherence in GIGHAART
- Preventable complications in CPCRA 064
- Future research???

CD4-VL Disconnect:
Can Impaired Fitness Be Used Strategically?



Deeks. *J Infect Dis* 2000;181:946.

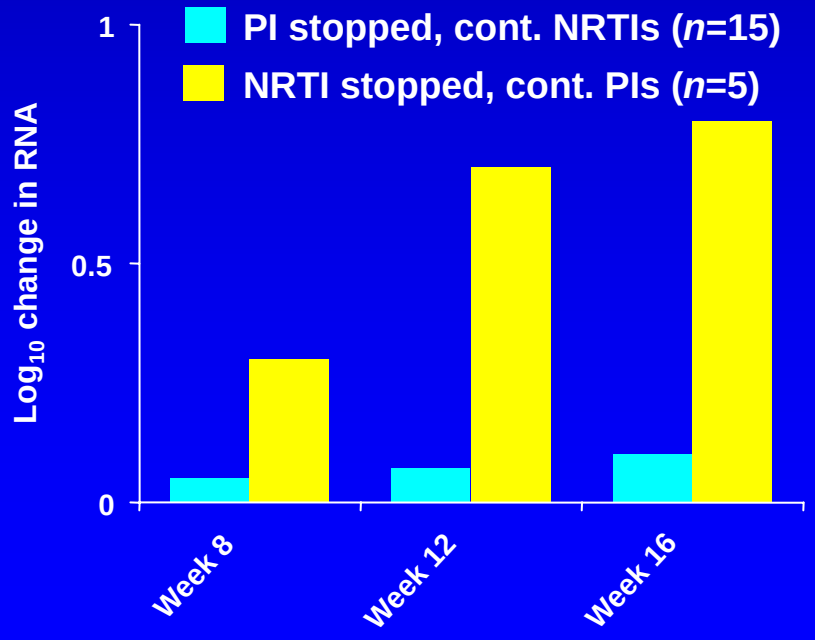
Continued Therapy in Patients With Virologic Failure: A Delicate Balance

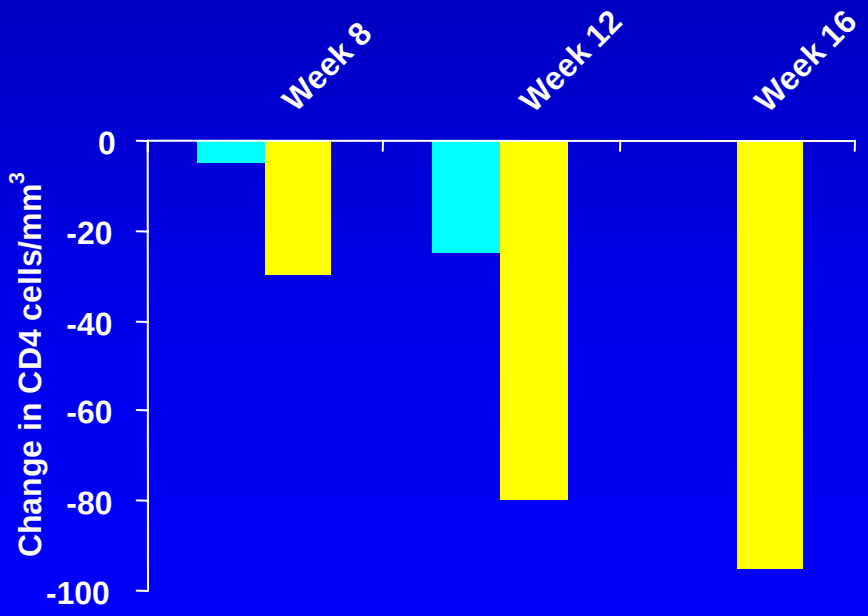


Partial Treatment Interruption

Observational study in clinically stable patients with limited treatment options (extensive resistance, drug toxicity):

- Patients on NRTI + PI regimens discontinued either NRTIs or PIs





Adapted from Deeks SG, *et al*. *10th CROI*, Boston 2003, #640

Partial Treatment Interruption

- Data are from small observational studies
- Reasons for interruption varied
- Resistance not equal across classes
- Results somewhat counterintuitive
  - » Protease mutations expected to have greater impact on fitness than TAMs
- Controlled trials needed

Treating the Highly Resistant Patient

- A patient with extensive treatment experience
- CD4 count 189, VL 64,000
- Cumulative
  - NRTI: 6 TAMs + M184V
  - NNRTI: 103N
  - PI: mutations at 30, 63, 77, 82, 90

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- Which class of drugs is most likely to be suppressive?
- Which class of drugs should you use next?

While Waiting for Suppressive Options…

What is the simplest, best tolerated regimen I can given that will maintain clinical and immunologic stability while minimizing the accumulation of new mutations?

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- RC often consistent with clinical observations (e.g. low RC in patient doing well despite failure)
- It's a great freebie, but would you pay extra for it?
  - » RC only relevant when you can't suppress virus
  - » How does RC on therapy compare with patient's baseline?
  - » How do you reduce RC in clinical practice?

Use of Investigational Drugs

Investigational Antiretroviral Agents: Use in Patients with Resistant Virus

Drug	Class	Active Against
D-D4FC	NRTI	NRTI-resistant virus (not Q151M, T69ins)
SPD 754	NRTI	NRTI-resistant virus
Capravirine	NNRTI	K103N, some double mutants
TMC 125	NNRTI	K103N, Y181C, most double mutants
Tipranavir	PI	PI-resistant virus w/ $\leq$ 2 PRAMs (33, 82, 84, 90)
TMC 114	PI	PI-resistant virus
Multiple	Entry inhibitors	NRTI-, NNRTI-, and PI-resistant virus

Coreceptor Antagonists

- CCR5 antagonists
  - » Risk of selection of X4 virus
  - » Exclusion of patients with X4 or dual-tropic virus, which are more common in patients needing salvage regimens
  - » Sensitivity of current coreceptor tropism assays
- CXCR4 antagonists
  - » Is there benefit without concomitant use of CCR5 antagonist?
- Combination therapy
  - » CCR5 antagonists are in more advanced phases of testing

A Familiar Salvage Scenario: "RESCUVIR®"

- RESCUVIR®: Active against all known PI-resistant virus, except with the rare 63Z mutation
- Phase III trial candidates: patients failing a PI-based regimen
- 1:1 Randomization:
  - » RESCUVIR® + OB vs.
  - » RTV-boosted PI + OB
- ENF allowed
- NNRTIs excluded because of drug interactions

Problems that Affect Enrollment

- Candidates are already failing what is often optimal PI-based therapy
- NNRTI exclusion means that most candidates will be NNRTI-resistant
- NNRTI & PI resistance/experience means that most will have some degree of NRTI resistance
- Many clinicians would otherwise be inclined to use “double-boosted PI” + ENF +/- NRTIs
- Protocol does not allow double-boosted PIs

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- Protocol does not allow double-boosted PIs
- ► 50% chance of being on ENF with unreliable OB regimen

Outcome

- Patients who *can* afford to wait for availability of 2nd generation agent aren't referred for enrollment (to avoid "wasting" ENF)
- Patients who *can't* afford to wait (e.g., those with very low CD4 and extensive resistance) are referred out of desperation, but will have poorer response to therapy
- Ideal "niche" patients (e.g. active NRTIs available, LPV/r susceptible) are few and far between

2004, 1999, 1989… What's the Difference?

- Review of recent request for T-20 through Maryland ADAP
- Patient with high-level genotypic and phenotypic resistance to NRTIs, NNRTIs, PIs
- CD4 189, VL 43,000
- Proposed background regimen: ATV + FTC

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- Patient with high-level genotypic and phenotypic resistance to NRTIs, NNRTIs, PIs
- CD4 189, VL 43,000
- Proposed background regimen: ATV + FTC
- Rationale: *"Fuzeon will be combined with 2 new drugs"*

“Salvage Therapy Only Works When it’s Not Really Salvage Therapy”

-Joep Lange