Agenda and Speakers

- Introductions, Background and Overview of Maraviroc
  Michael Dunne MD, Therapeutic Area Head, Development, Infectious Diseases
- Clinical Efficacy
  Howard Mayer MD, Global Clinical Leader, Pfizer
- Safety and Toleration
  Steve Felstead MB ChB, Maraviroc Team Leader, Pfizer
- ***In Vitro*** **and** ***In Vivo*** **Tropism and Resistance Evaluation**
  Mike Westby PhD, Virology Team Leader, Pfizer
- Medical Need and Place in HIV Armamentarium
  Dan Kuritzkes MD, Brigham and Women's Hospital, Harvard Medical School, Boston
- Conclusions
  Michael Dunne MD

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Tropism and Resistance

Mike Westby, PhD

Pfizer Global Research and Development

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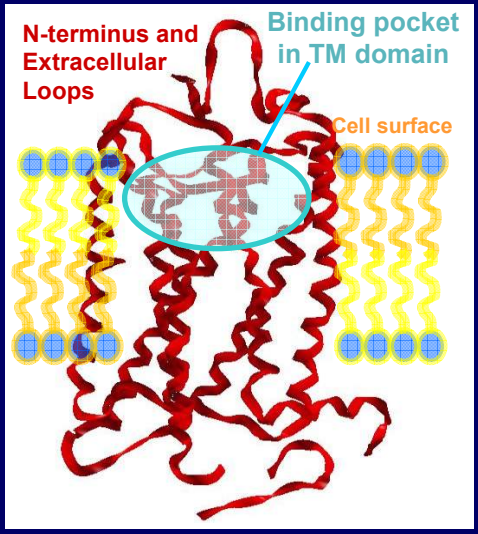
Viral Escape to Maraviroc will be Different from Anything Seen Previously

Maraviroc:

- Binds to a host protein (all other ARV have viral targets)
- Only active against CCR5-tropic strains
- Not a competitive inhibitor



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Virology Issues Relevant to the Proposed Indication

- For patients in whom CXCR4-using virus is detected, does virus emerge by:
  - Mutation of a CCR5-tropic virus (co-receptor switch)?
  - Detection on-treatment of a pre-existing CXCR4-using subpopulation?
- For patients failing with a CCR5-tropic virus:
  - Look for evidence/incidence of maraviroc resistance
  - What are the phenotypic and genotypic markers of maraviroc resistance?

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Mechanism of Tropism Changes in the Clinical Program

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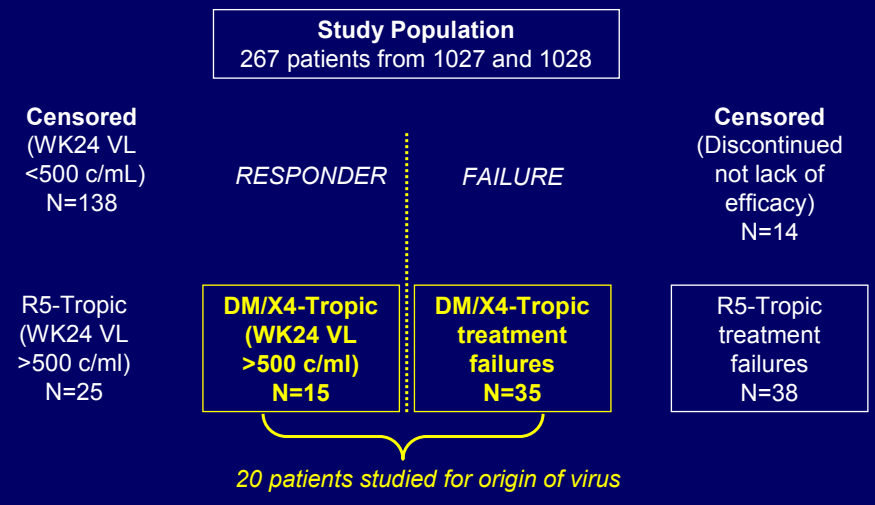
Population Studied for Shifts in Tropism in Phase 3 Clinical Program



Excludes 2 patients whose virus was NR at Wk24/failure

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Strategy to Understand Changes in Tropism Occurring on Treatment

- Viral co-receptor tropism and sequencing performed on:
  - 192 Env clones at baseline (to look for CXCR4-using viruses present at a low incidence)
  - 48 Env clones on-treatment
- V3 alignments and phylogenetic trees constructed to compare pre- and on- treatment viruses

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Summary of Findings on Tropism Changes Occurring on Treatment

- No evidence of a switch in viral tropism in vivo
  - CXCR4-using Env clones detected at baseline
  - On-treatment CXCR4-using clones genetically distinct from CCR5-tropic clones
- No mechanistic differences in origin of CXCR4 using virus seen between maraviroc and placebo patients
- Changes in tropism were seen in absence of treatment failure

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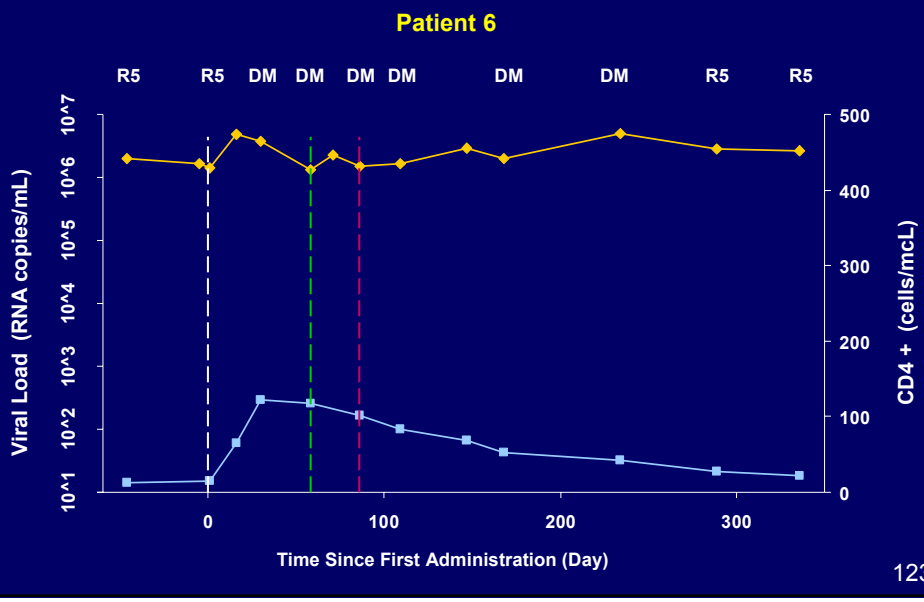
Example of a Patient Whose Virus was R5-tropic at Baseline



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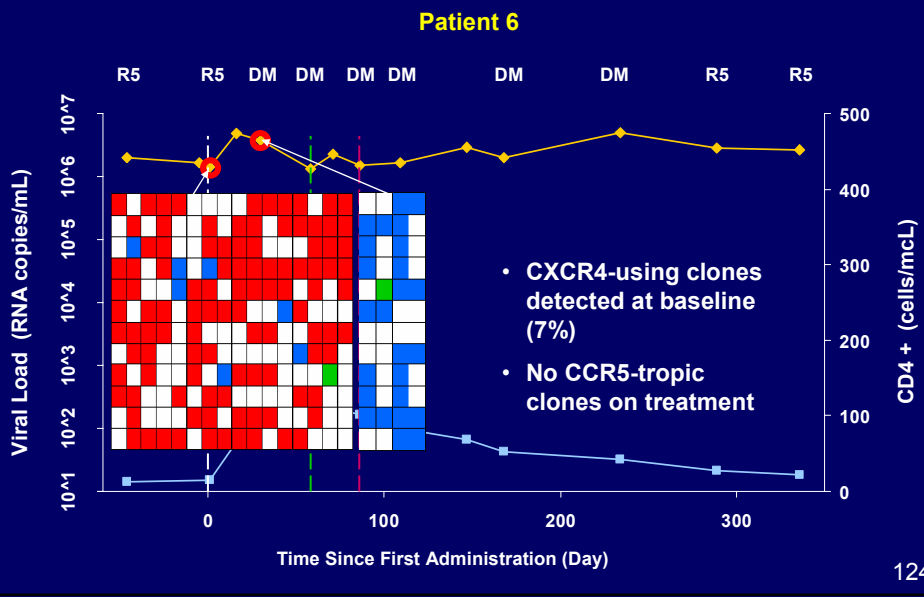
CXCR4-using Env Clones Were Detected at Low Frequency in the Baseline Sample



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Pre- and On-treatment CXCR4-using Clones Share V3 Sequence

Patient 6

Visit	V3 Sequence	Trofile™
BL	CTRLNNNTRRSITIGPGRAFYTSDIIGNIRQAHC	R5
	.....R...	R5
	.....A.....D.....	R5
	.....D.....	R5
	.....K.M.L...KV...TGT.....	DM
	.....K.M.L...KV...TGT.....	DM
	.....K.M.L...KV...TGT.....	DM
WK4	.....K.M.L...KV...TGT.....	DM
	.....K.M.L...KV...TGT.....	DM
	.....K.M.L...KV...TGT.....	DM
	R.....K.M.L...KV...TGT.....	DM
	.....K.M.L...KV...TGT.....	DM

Data consistent with CXCR4-using clones pre-existing maraviroc treatment

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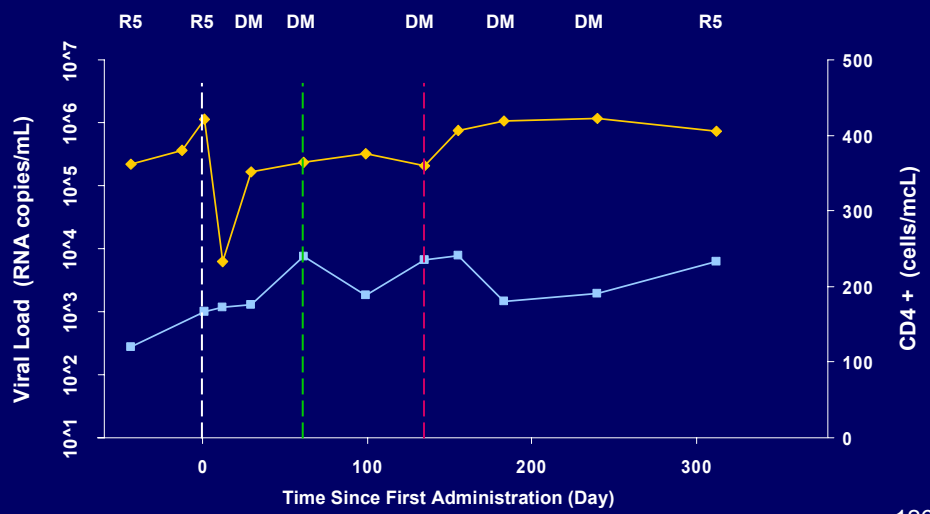
Example of a Patient Whose Virus was R5-tropic at Baseline

Patient 8



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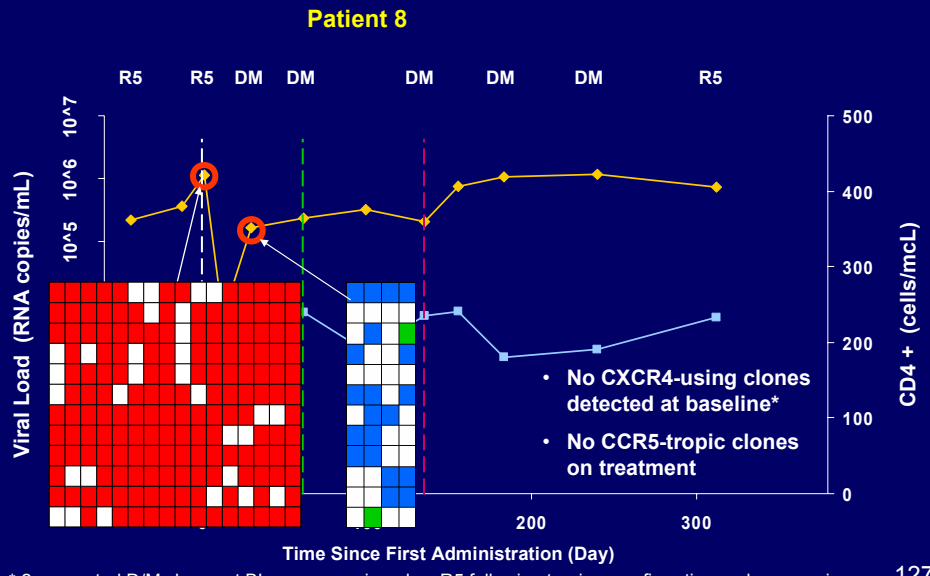
No CXCR4-using Env Clones Were Detected in the Baseline Sample



* 2 suspected D/M clones at BL were reassigned as R5 following tropism confirmation and sequencing

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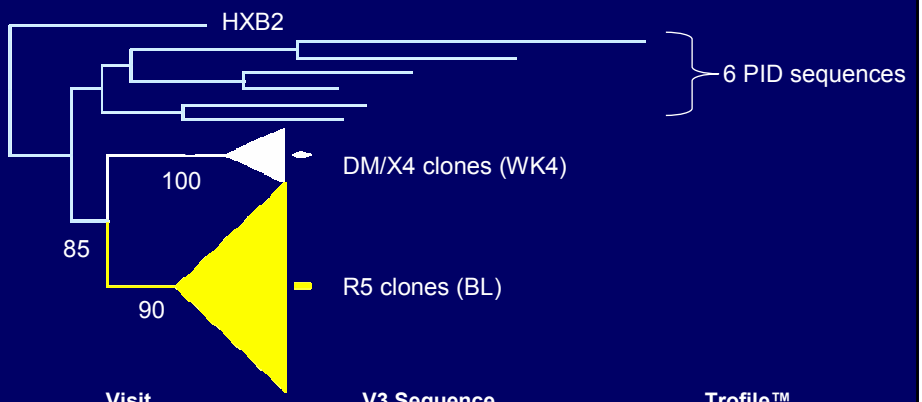
CCR5-tropic Clones and CXCR4-using Clones are Phylogenetically Distinct



Visit	V3 Sequence	Trofile™
BL	CTRPNNNT-RKSIPMGPG--QAIYATGAIIGDIRQAHC	R5
WK4	........R..-.HI..RH..VM...E-...N......	DM

0.1

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Characterization of Maraviroc Resistance

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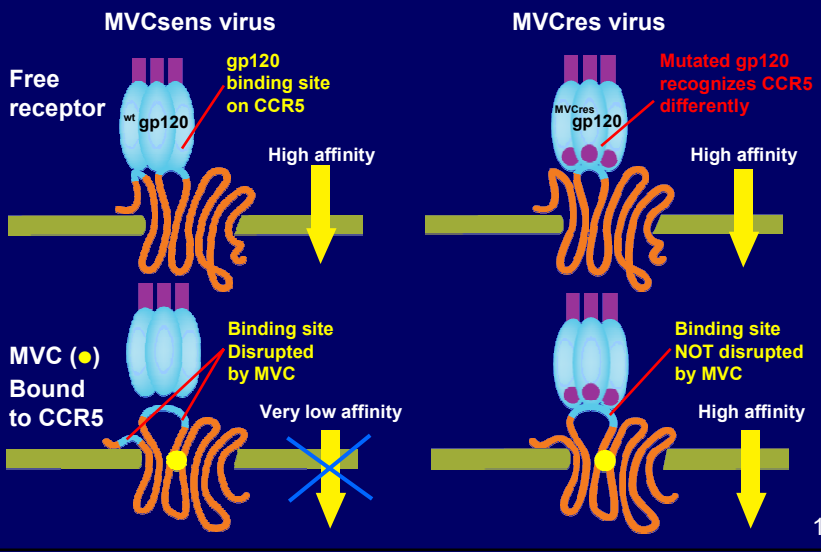
Maraviroc Resistant Virus Recognises Compound-Bound Receptors



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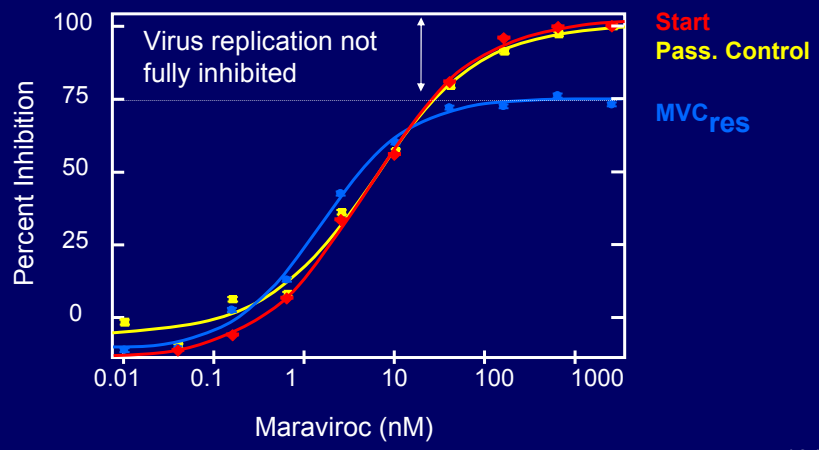
Maraviroc Resistant Virus Remained CCR5-tropic but Cannot be Fully Inhibited at High Concentrations

*MVC resistant CC1/85 tested in PhenoSense HIV Entry Assay**



**Env-recombinant, Pseudovirus Drug Susceptibility assay (CD4+CCR5+U87 cells)*

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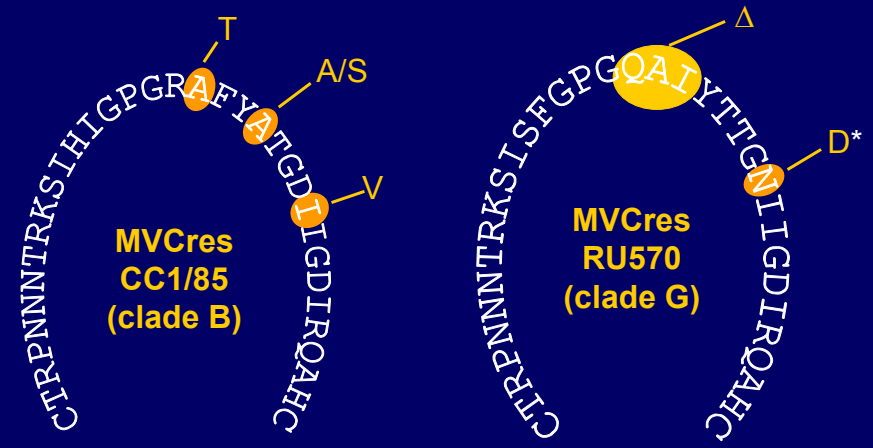
Amino Acid Substitutions/Deletions were Selected in the Gp120 V3 Loop



* Also selected in drug-free control culture

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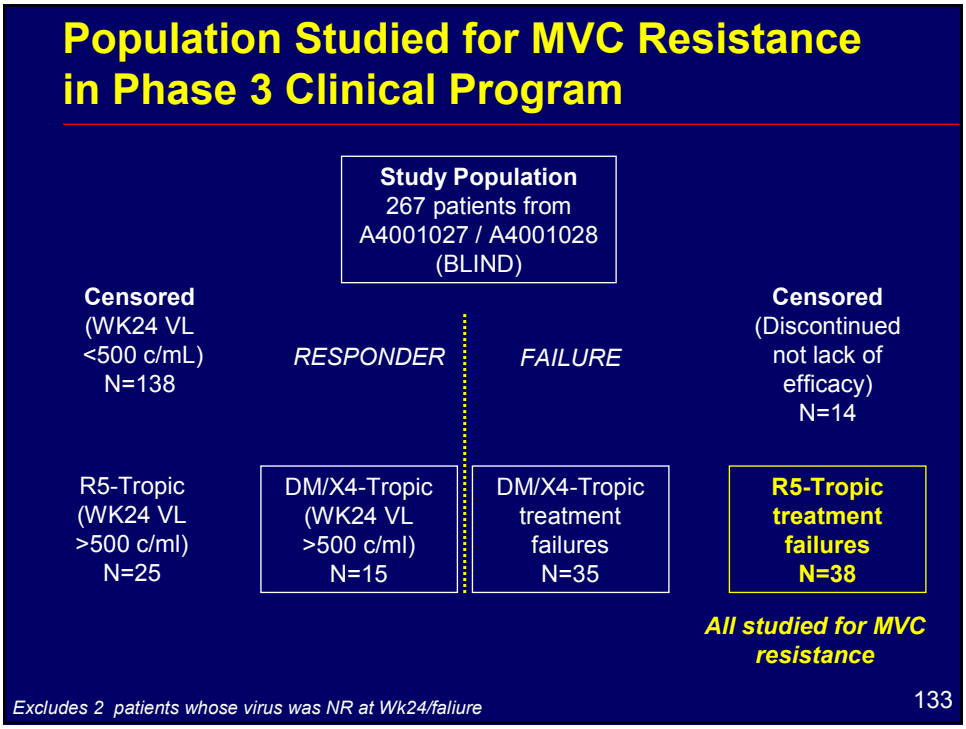
Population Studied for MVC Resistance in Phase 3 Clinical Program



Excludes 2 patients whose virus was NR at Wk24/faliure

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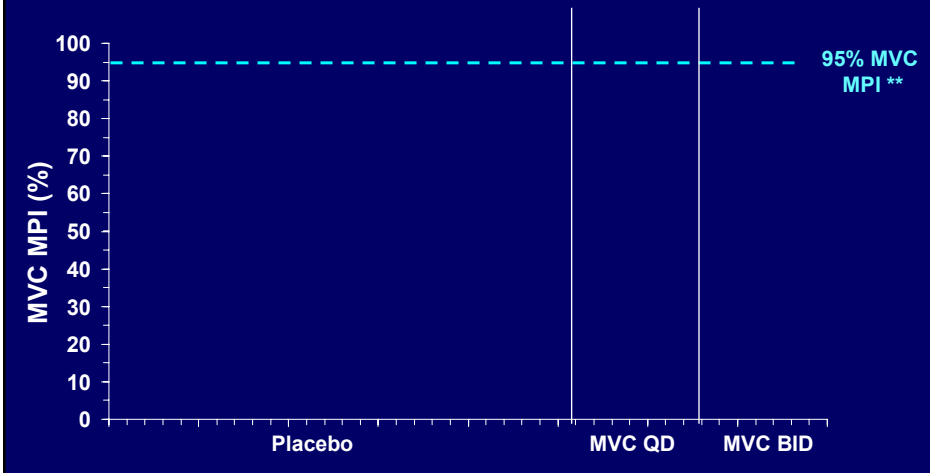
MVC Susceptibility for all R5 Failures (n=37*) – Blinded Analysis of 267 Cohort



Data obtained using PhenoSense HIV Entry Assay

* Excludes one R5 failure (MVC arm) for whom no valid susceptibility data was obtained
** Pre-determined based on pre-clinical findings

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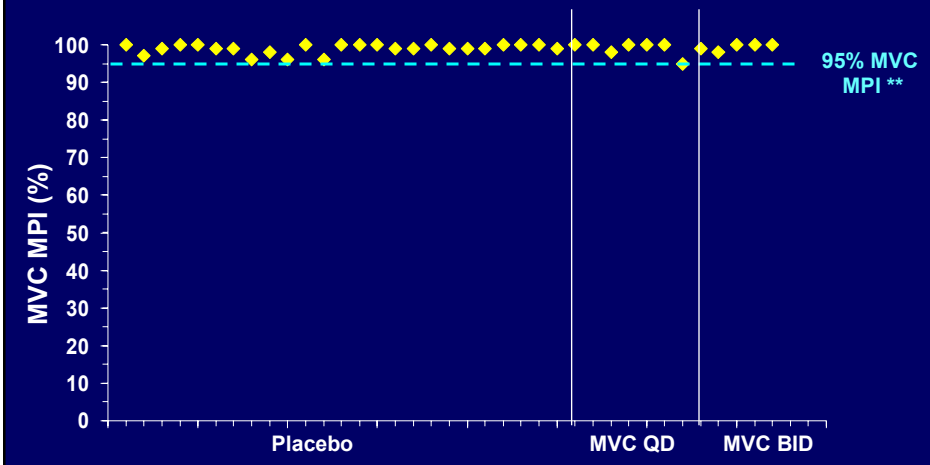
No Viruses were Resistant at Baseline



Data obtained using PhenoSense HIV Entry Assay

** Pre-determined based on pre-clinical findings

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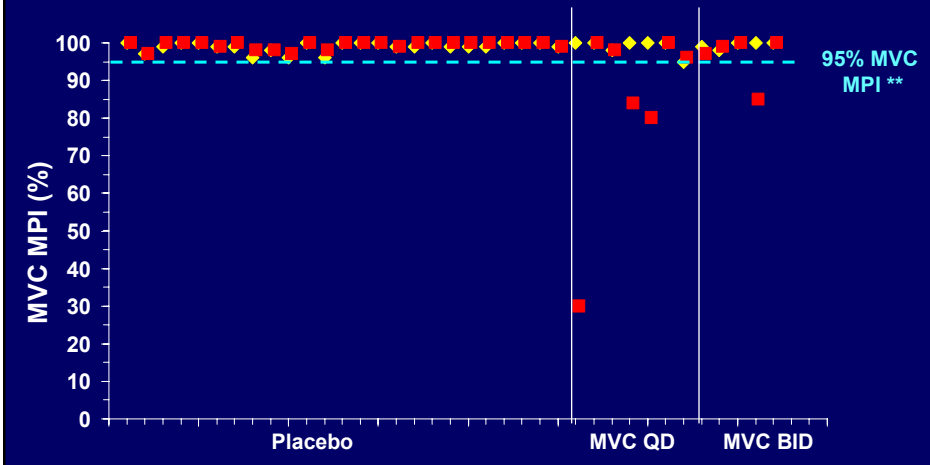
Reduced MPI <95% Seen in Four Patients Failing Blinded Therapy



Data obtained using PhenoSense HIV Entry Assay

** Pre-determined based on pre-clinical findings

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Mutations in the V3 Loop Play a Key Role in Conferring MVC Resistance

PID	Clone ID	MPI (%)	V3 sequence (10 20 30)
8	BL	100	CTRPNNNTRKSIPIG-PGRAFYATGDIIGDIRQAHC
	BL (SDM V3 Fail)	41	S A
	FAIL	51	S A
	FAIL (SDM V3 BL)	98	
14	BL	100	CTRPGNNTRKSIHMGPGSSIYATGAIIGDIRQAHC
	BL (SDM V3 Fail)	85	F DV
	FAIL	63	F DV
	FAIL (SDM V3 BL)	99	
4	BL	100	CTRPNNNTRKGIHIGPGRSFYATGDIIGDIRQVHC
	BL (SDM V3 BL)	100	S V
	FAIL	55	I S V A
	FAIL (SDM V3 BL)	99	I A
1	BL	96	CIRPNNNTRKSINIGPGRAWYTTGDIIGDIRQAHC
	BL (SDM V3 Fail)	66	H
	FAIL	50	T H K A
	FAIL (SDM V3 BL)	91	T K A

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Summary of Findings on Maraviroc Resistance

- Pre-clinical and clinical data is consistent with non-competitive mechanism of action
- Dose response curves with plateaus in MPI are a phenotypic marker of maraviroc resistance
- Mutations in the gp120 V3 loop play a key role in conferring maraviroc resistance

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Conclusions

- CXCR4-using virus is detected in approximately two thirds of patients who fail therapy with maraviroc
  - Intensive clonal analyses support the emergence of CXCR4-using viruses as being a consequence of selective suppression of CCR5-tropic clones by maraviroc
  - This is further supported by the reversion to R5-tropism in patients during subsequent off-drug follow-up

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Conclusions

- In patients failing with CCR5-tropic virus, maraviroc resistance was detected in approximately 30% (4/12) patients studied
  - Multiple pathways to MVC resistance were described
  - The correlation between markers of maraviroc resistance and clinical outcome will continue to be investigated
- Collectively the virology studies supports maraviroc acting as a highly selective and potent inhibitor of CCR5-tropic viruses

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- *In vitro* and *in vivo* Tropism and Resistance Evaluation
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  Michael Dunne MD

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