HIV Treatment bnAbs: Clinical Research Considerations

October 30th, 2023

Lessons from CCR5 Antagonists

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Labcorp - Monogram Biosciences

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Outline

- Requirement of a screening assay for the use of CCR5 antagonists
- Positive and negative predictive value of the Trofile assay in CCR5 antagonist trials
- Minor populations of CXCR4-using variants associated with treatment failure
- Enhanced detection of CXCR4-using variants improves clinical utility
- Reduced maximal percent inhibition can be associated with treatment failure
- Envelope complexity - challenges for genotypic assay development
- Partnering for international commercialization of a coreceptor tropism assay
- Barriers to CCR5 antagonist uptake
- Adapt testing to treatment paradigms – viremic (RNA) -> suppressed (DNA)

Contributions to CCR5 antagonist development

- Monogram has supported the development and clinical use of many HIV therapeutics including CCR5 antagonists, other entry inhibitors and bnAbs
  - Coreceptor engagement
    - CXCR4: Plerixafor (AMD3100), AMD11070, CXCR4 antagonists; AnorMED
    - CCR5: Maraviroc, CCR5 antagonist (Selzentry, UK-427,8570); Pfizer

      Vicriviroc, CCR5 antagonist (Sch-417690, Sch-D); Schering-Plough

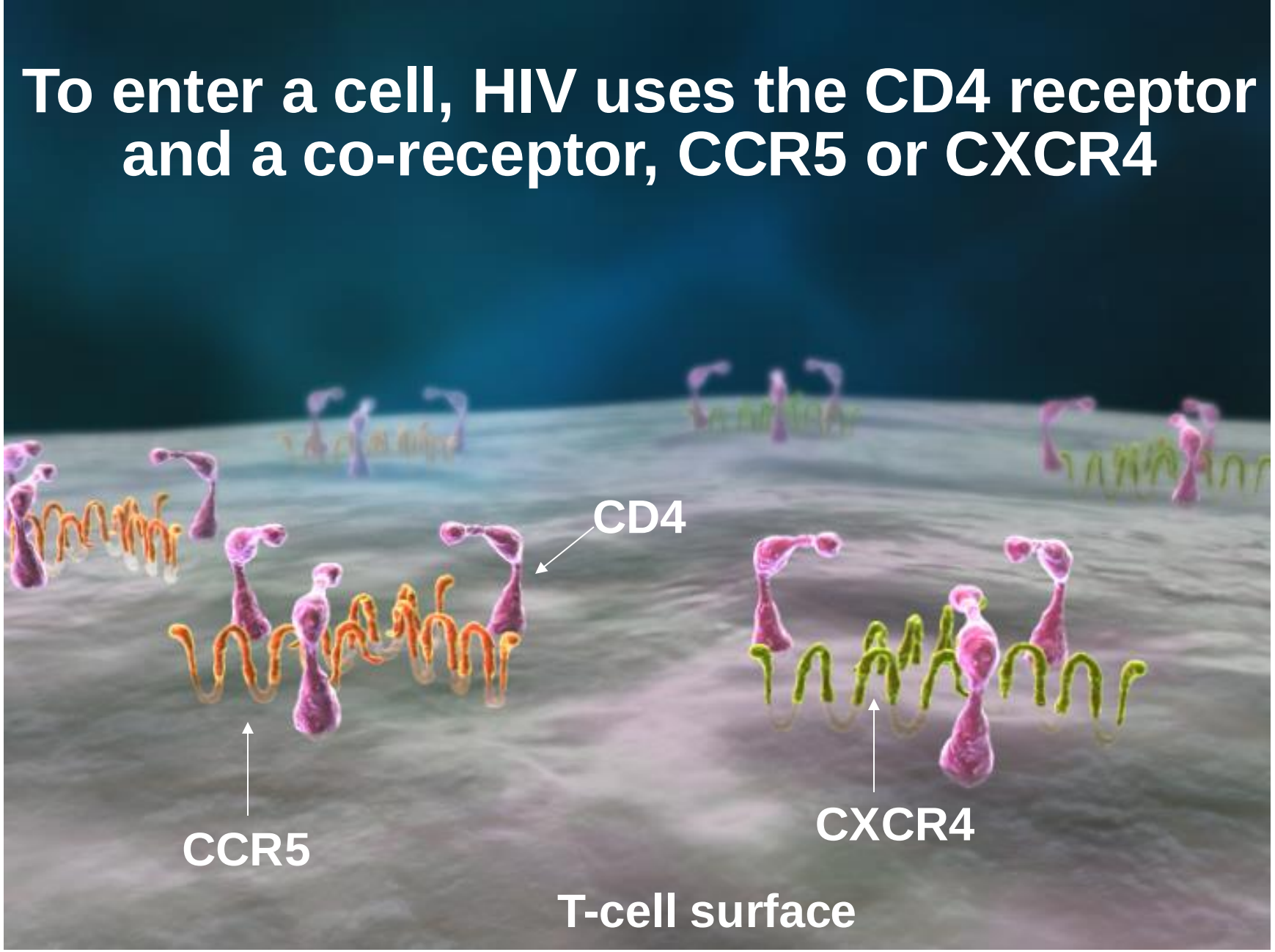
      Aplaviroc, CCR5 antagonist (GW-873,140); GSK

      Leronlimab, CCR5 mAb (PRO 140); Progenics/Cytodyn

      Cenicriviroc; CCR2/CCR5 antagonist; Tobira
  - Membrane fusion
    - gp41: Enfuvirtide, peptide (Fuzeon, T20), T1249; Trimeris/Roche
  - Attachment
    - CD4: Ibalizumab, CD4 mAb (Trogarzo, TNX-355); Tanox/TaiMed/Theratechnologies

      UB-421, CD4 mAb; United Biomedical Inc.
    - gp120: Fostemsavir, (Rukobia, BMS-488,403); BMS/ViiV

To enter a cell, HIV uses the CD4 receptor and a co-receptor, CCR5 or CXCR4



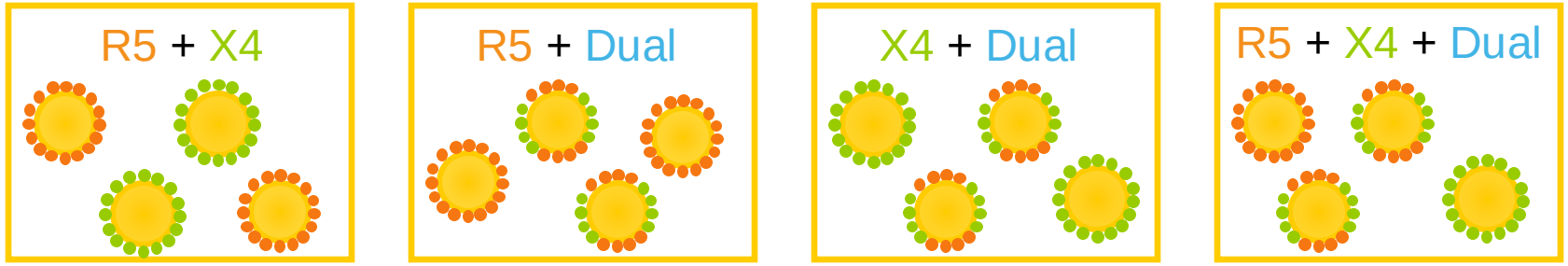
Tropism definitions

R5 HIV — Uses the CC**R5** co-receptor ONLY

X4 HIV — Uses the C**X**CR**4** co-receptor ONLY

Dual HIV — Can use either co-receptor

Mixed — A viral population with 2 or more tropisms



- R5 viruses predominant early in infection
- CXCR4-using viruses (D/M, X4) can develop later in infection

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Coreceptor tropism of 6857 samples from treatment naïve and experienced individuals

			R5	D/M	X4
MOTIVATE 1 & 2[4]	Experienced	2560	56%	41%	3%
TORO 1/2[5]	Experienced	612	50%	46%	4%
ACTG 5211[6]	Experienced	391	49%	47%	4%
SCOPE[7]	Experienced	186	60%	39.5%	0.5%
HOMER cohort[1]	Naive	979	82%	18%	<1%
C & W cohort[2]	Naive	402	81%	19%	<1%
Demarest[3]	Naive	299	88%	12%	0%
Pfizer 1026[4]	Naive	1428	85%	15%	<1

1Brumme ZL, et al. *J Infect Dis.* 2005;192:466-474.
2Moyle GJ, et al. *J Infect Dis*. 2005;191:866-872.
3Demarest J, et al. *ICAAC* 2004. Abstract H-1136.
4Coakley E, et al. 2nd Viral Entry Workshop, Abstract 8
5Melby et al 13th *CROI 2006* Abstract 233.
&Wilkin T, et al. *CROI* 2006. Abstract 655.
7Hunt et al. *J Infect Dis*. 2006;194:926-30

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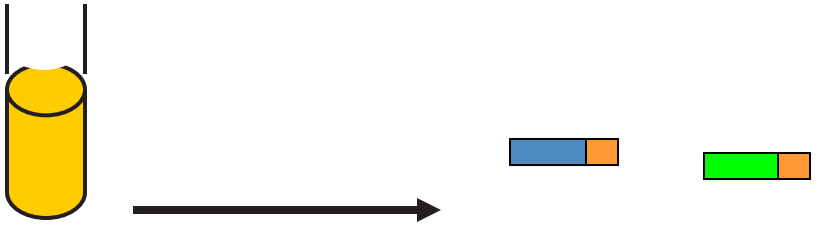
Maraviroc PI – Test for R5-tropic HIV prior to initiation of CCR5 antagonist

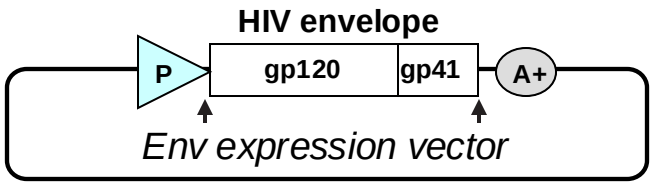
- Prior to initiation of SELZENTRY for treatment of HIV-1 infection, test all patients for CCR5 tropism using a highly sensitive tropism assay. SELZENTRY is recommended for patients with only CCR5-tropic HIV-1 infection. Outgrowth of pre-existing low-level CXCR4- or dual/mixed-tropic HIV-1 not detected by tropism testing at screening has been associated with virologic failure on SELZENTRY [see Microbiology (12.4), Clinical Studies (14.1)]. (Updated 9/2022)

Trofile HIV coreceptor tropism assay

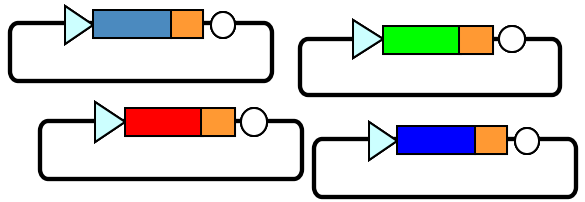
Patient plasma or serum sample



Amplify full length HIV *envs* by RT-PCR

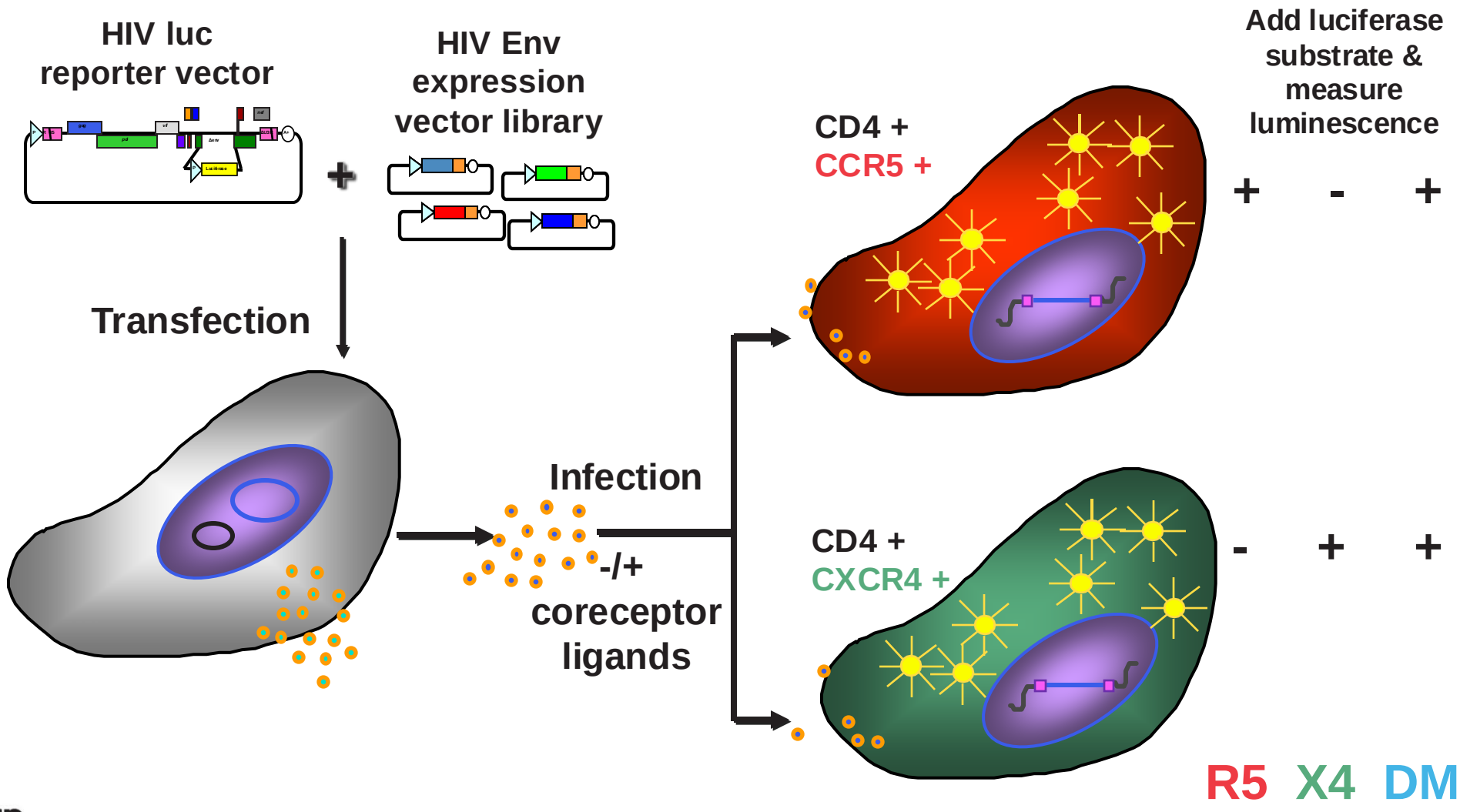


Clone *envs* into Env expression vector



Patient Env expression vector library

Trofile HIV coreceptor tropism assay



Trofile Report

trofile™
CO-RECEPTOR TROPISM ASSAY
biosciences
monogram

Patrick Joseph, MD, Medical Director - 345 Oyster Point Blvd
South San Francisco, CA 94080 - Tel: (800) 777-0177

Patient Initials:	DOB	Patient ID	Gender	Monogram Accession # **05-102196**
Date Collected	Date Received	Date Reported	Mode	Report Status
Investigator			Specimen ID	
Comments:				

Tropotype Result

R5 D/M X4

Virus uses CCR5 co-receptors in the process of cell entry.

R5

Activity of CCR5 antagonist anticipated?

■ YES
□ NO

ABOUT TROPISM

TROFILE™— A HIGHLY SENSITIVE TROPISM ASSAY

Trofile is a cell-based approach to determine a patient's HIV co-receptor tropism (or "Tropotype™"). Trofile uses the complete gp160 coding region of the HIV-1 envelope protein ensuring that all of the determinants of tropism are tested. CLIA* validation experiments demonstrate that Trofile is 100% sensitive at detecting 0.3% CXCR4-using minor variants.

TROFILE VIRAL CLASSIFICATION

Co-receptor tropism is defined as an interaction of a virus with a specific co-receptor on the target cell. To gain entry into CD4+ cells, HIV must bind to the cell surface CD4 receptor and to one of two co-receptors, CCR5 or CXCR4.

CCR5 Tropic (R5) HIV-1
Virus uses CCR5 to enter CD4+ cells.

CXCR4 Tropic (X4) HIV-1
Virus uses CXCR4 to enter CD4+ cells.

DUAL/MIXED Tropic (D/M) HIV-1
Dual-tropic viruses can use either CCR5 or CXCR4 to enter CD4+ cells. Mixed-tropic populations contain viruses with two or more tropisms.

Non-reportable
Co-receptor tropism could not be determined by the Trofile assay. Common causes of a non-reportable result are viral load <1,000 copies/mL, reduced viral fitness, or compromised sample collection/handling.

CCR5 CO-RECEPTOR ANTAGONISTS

This class of drugs binds to CCR5 and blocks CCR5-mediated HIV entry into host cells. Trofile is used to determine whether a CCR5 antagonist may be an appropriate drug for a patient. Several clinical trials of CCR5 antagonists have demonstrated the positive and negative predictive value of Trofile in clinical settings.

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Clinical Utility of Trofile: Positive Predictive Value

- MOTIVATE 1 & 2—In populations with ≥ 3-class ARV experience and/or 3-class resistance, maraviroc demonstrated significant antiviral activity to week 48 in individuals harboring R5 virus by the Trofile™ assay
  - VL reduction 1.84 $\log_{10}$ copies/mL vs 0.79 with placebo ($p < 0.001$)

- ACTG5211—In a population with advanced disease and high levels of drug resistance, vicriviroc demonstrated significant antiviral activity to week 24 in individuals harboring R5 virus by the Trofile™ assay
  - R5 at entry (n = 71)
  - VL reduction 1.83 $\log_{10}$ copies/mL ($p = 0.001$)

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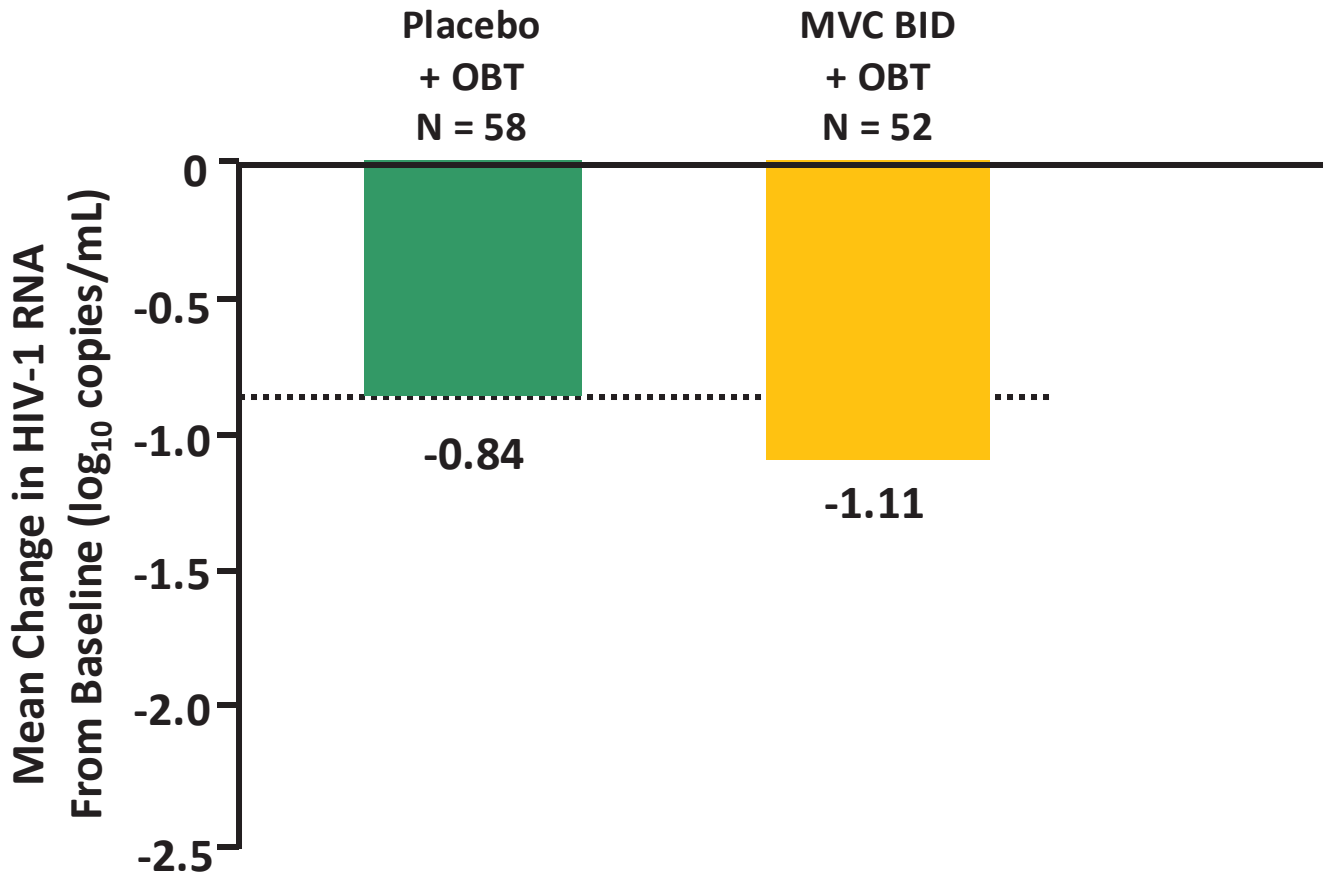
Clinical Utility of Trofile: Negative Predictive Value

- 1029 — In a population of antiretroviral-experienced individuals designated D/M at entry by the Trofile assay, the addition of maraviroc (MVC) to OBT did not provide added antiviral activity at week 48



Saag M, et al. *J Infect Dis*. 2009;199:1638-1647

Enhanced Sensitivity Trofile™ Assay

- 8-10% treatment experienced patients enrolled in clinical trials of vicriviroc and maraviroc had changes in tropism calls between screen (R5) and baseline (DM) samples, reflective of the presence of DM virus around the assay detection limit
  - These patients had a reduced virologic response compared to those with R5 at both screen and baseline
- An enhanced sensitivity Trofile assay was developed to increase minor CXCR4-using variant detection with the aim of further optimizing the selection of patients who may benefit from therapy with entry inhibitors targeting CCR5
- Clinical trial reanalysis was performed to evaluate if the enhanced Trofile assay would predict better virologic outcomes

Sensitivity to Detect Minor Variants

Select a pair of X4 and R5 clones with similar infectivity from 4 patients

↓

Prepare 18 mixtures for each Env clone pair

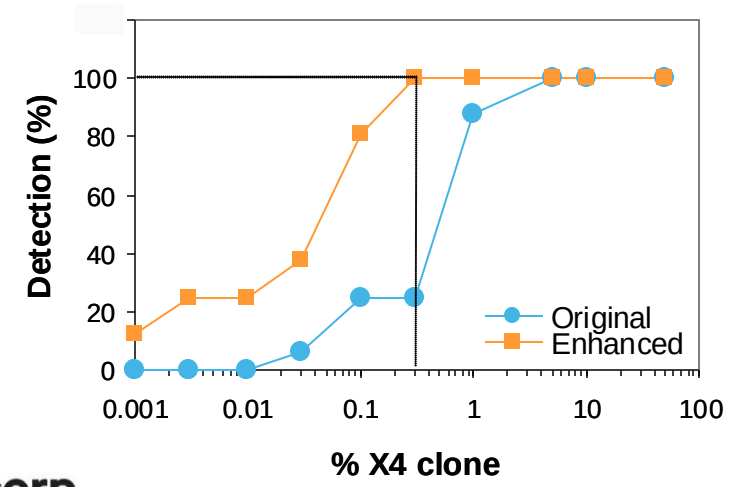
	% of clone in mixture																	
X4	0	0.001	0.003	0.01	0.03	0.1	0.3	1	5	10	50	90	95	99	99.7	99.9	99.99	100
R5	100	99.999	99.997	99.99	99.97	99.9	99.7	99	95	90	50	10	5	1	0.3	0.1	0.01	0

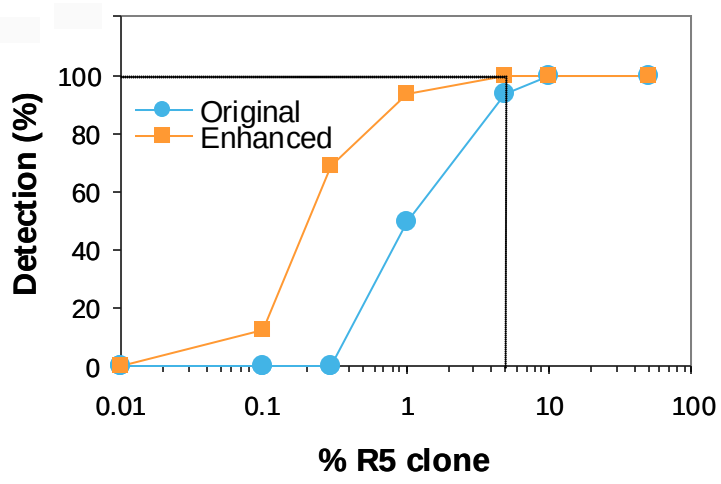
↓

Test each mixture in 4 independent standard and enhanced Trofile assays
(Total of 576 assays; 288 standard and 288 enhanced)

↓

Determine % X4 and R5 variant detection for each mixture





X4 variant detection:

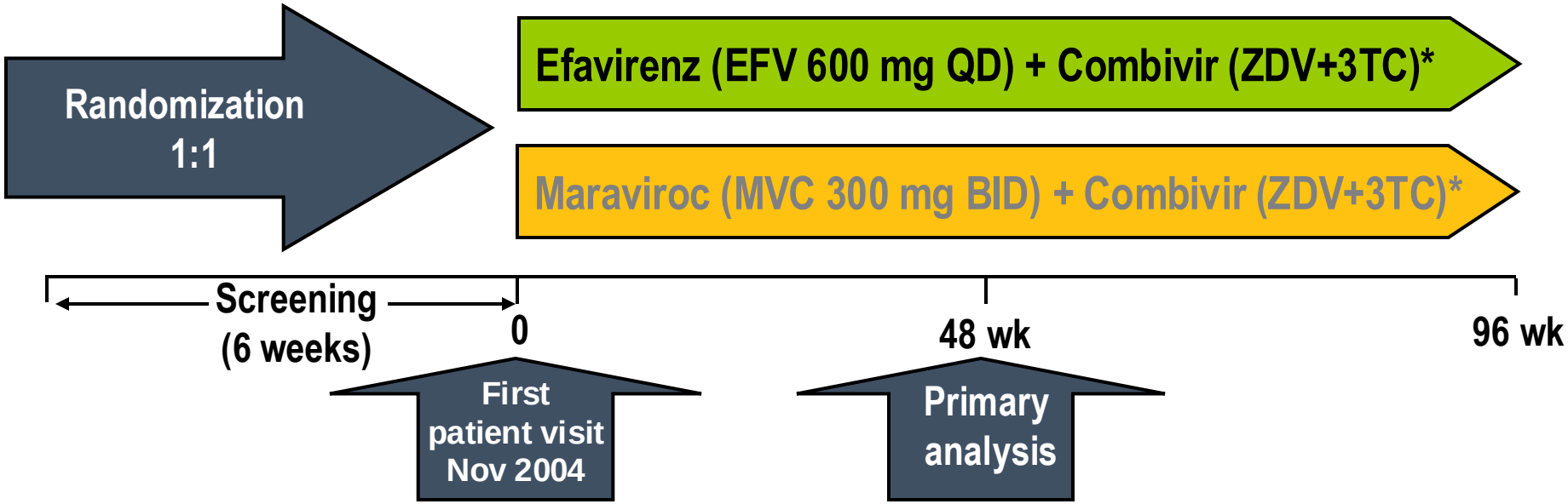
Original Trofile

100% at 10% mixture

Enhanced Trofile

100% at 0.3% mixture

MERIT Study: Phase 3 Trial Design



Patient eligibility criteria:

- ≥16 years of age
- Treatment naive
- R5 HIV-1 infection
- HIV-1 RNA ≥2,000 copies/mL
- No evidence of resistance to EFV, ZDV, or 3TC

Patients stratified by:

- HIV-1 RNA < and ≥100,000 copies/mL at screening
- Geographic location: Northern Hemisphere and Southern Hemisphere

MVC QD arm discontinued at end of Phase 2b (week 16) for failure to meet protocol-defined criteria to continue (205 pts completed 16 weeks)

***Patients experiencing toxicity to ZDV or 3TC were permitted to substitute an alternative NRTI**

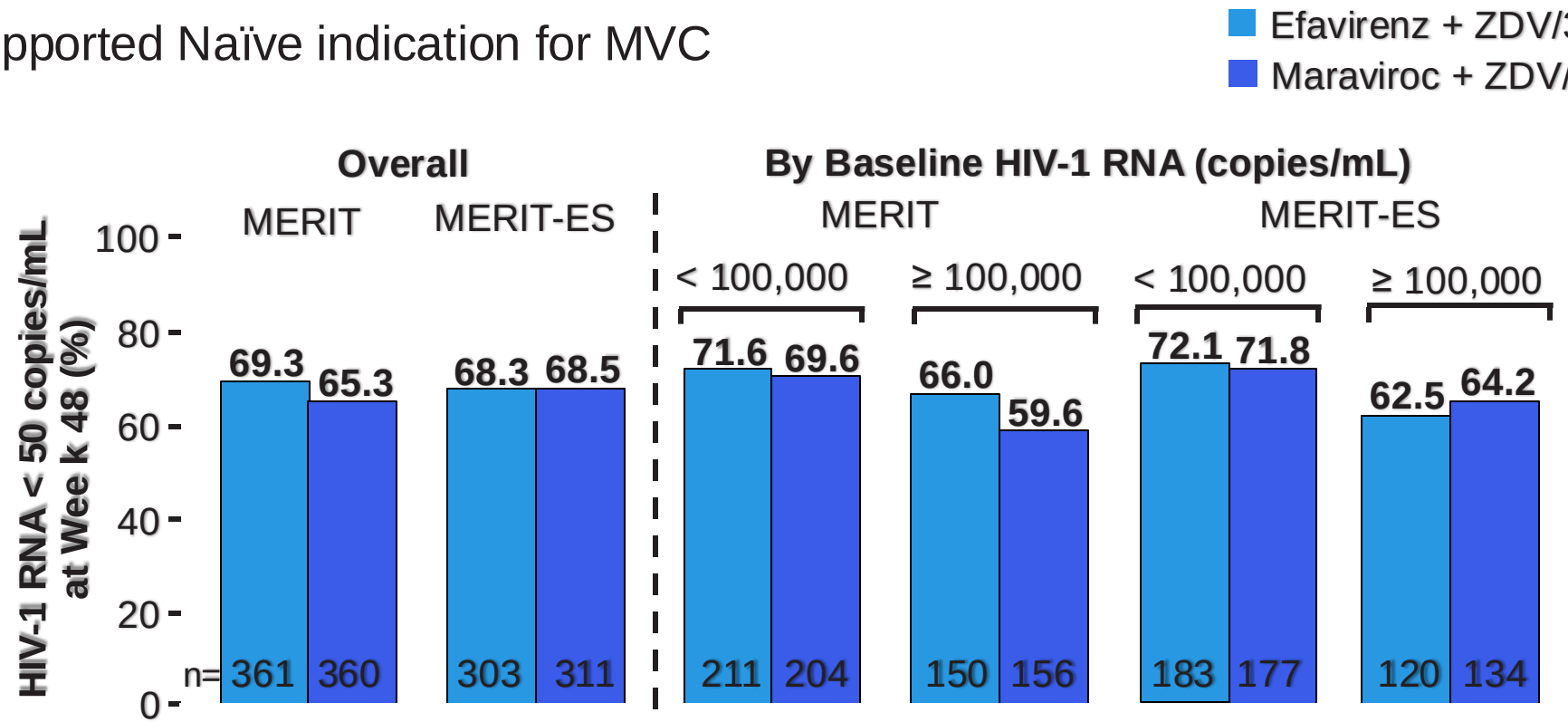
Saag M, *et al. 4th IAS* 2007. Abstract WESS104

Merit Outcome and Reanalysis with Enhanced Trofile

- Based on the pre-planned statistical analysis (noninferiority margin of –10%), MVC:
  - Did not meet the noninferiority margin at the <50 copies/mL endpoint (65.3% vs 69.3%)
  - Was noninferior to EFV based on <400 copies/mL endpoint (70.6% vs 73.1%)
- 58 subjects failed due to lack of viral efficacy in the original week 48 outcome analysis
  - 0 of 15 of the viral efficacy failures in the EFV arm were associated with a switch in tropism
  - 19 of 43 of the viral efficacy failures in the MVC arm were associated with a switch in tropism
- Enhanced sensitivity Trofile testing was performed using stored Env-expression vector pools on all 721 patients who tested R5-tropic by original Trofile assay
  - No clinical outcome information was available to Monogram
  - All analyses were pre-specified by Pfizer in a statistical analysis plan

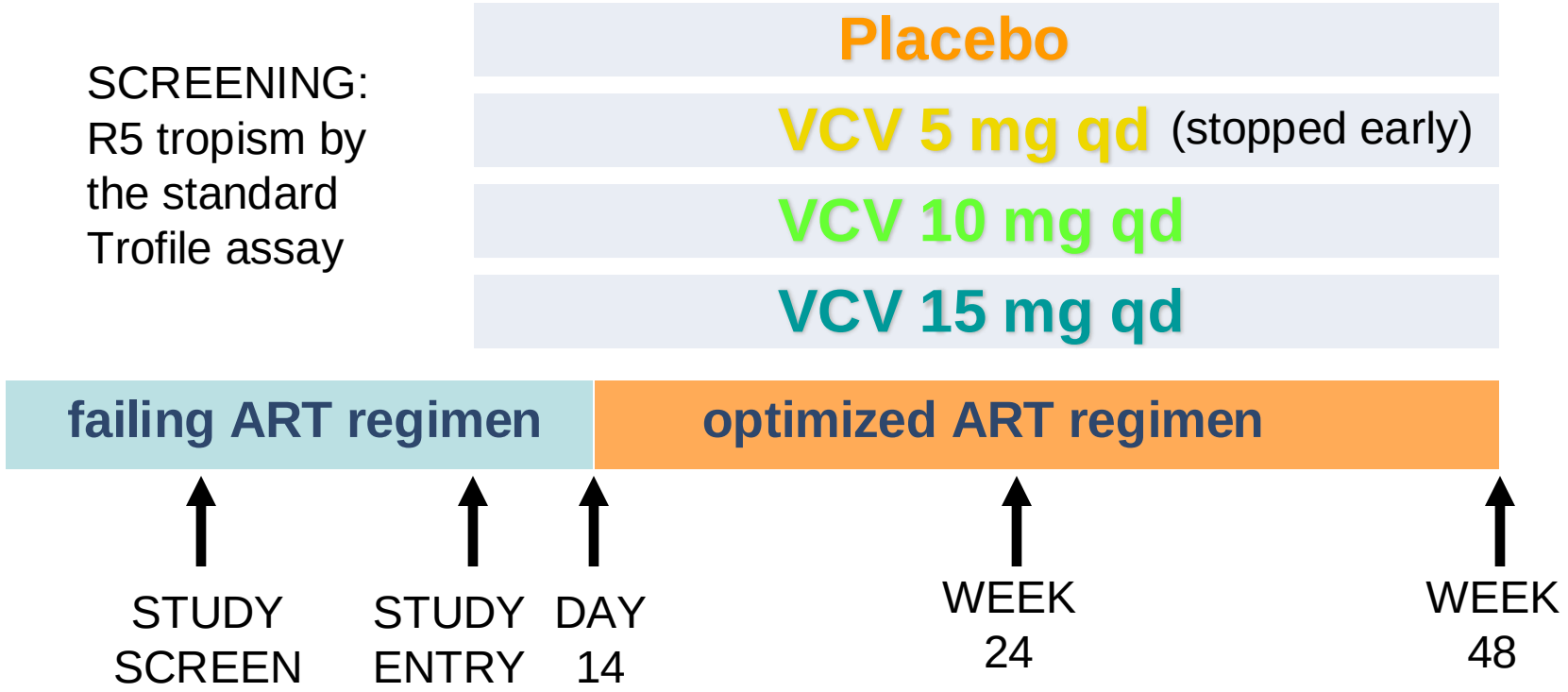
Reanalysis of Efficacy in MERIT with Enhanced Trofile

- The enhanced Trofile assay reclassified virus tropism to DM at screening in 15% of patients
  - Noninferiority criteria met (rates of HIV-1 RNA < 50 copies/mL) when patients with DM virus were excluded from study analysis
  - Supported Naïve indication for MVC



Saag M, et al. ICAAC/IDSA 2008. Abstract 1232a.

ACTG 5211 Study Design



- 118 subjects enrolled with R5 virus at screen by standard Trofile
- Stratified by: enfuvirtide use, CD4 <50 or >50 cells/µL
- All regimens included 100-800 mg RTV
- Virologic failure: <1 log10 ↓ in HIV RNA at/after 16 wks

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Gulick et al., JID 2007; 196: 304-312

Re-analysis ACTG 5211

- 12/118 (10%) individuals with R5 virus at screen had D/M virus detected at study entry using the original Trofile assay
  - D/M at entry portended attenuated response compared to R5 virus at screen and entry
    - R5-R5 -1.83 log10 HIV RNA Week 24 (n=71)
    - R5-DM -0.77 log10 HIV RNA Week 24 (n=10)

- An additional 18 R5-R5 individuals had CXCR4-using virus detected on study using the original Trofile assay

- The enhanced Trofile assay was used to reanalyze tropism at study screen and/or entry

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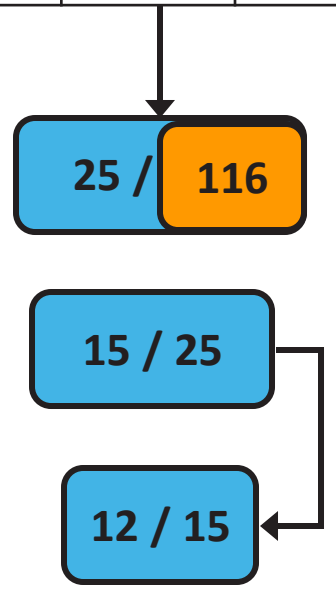
Reanalysis of ACTG 5211 VCV Trial Samples with an Enhanced Sensitivity Trofile™ Assay

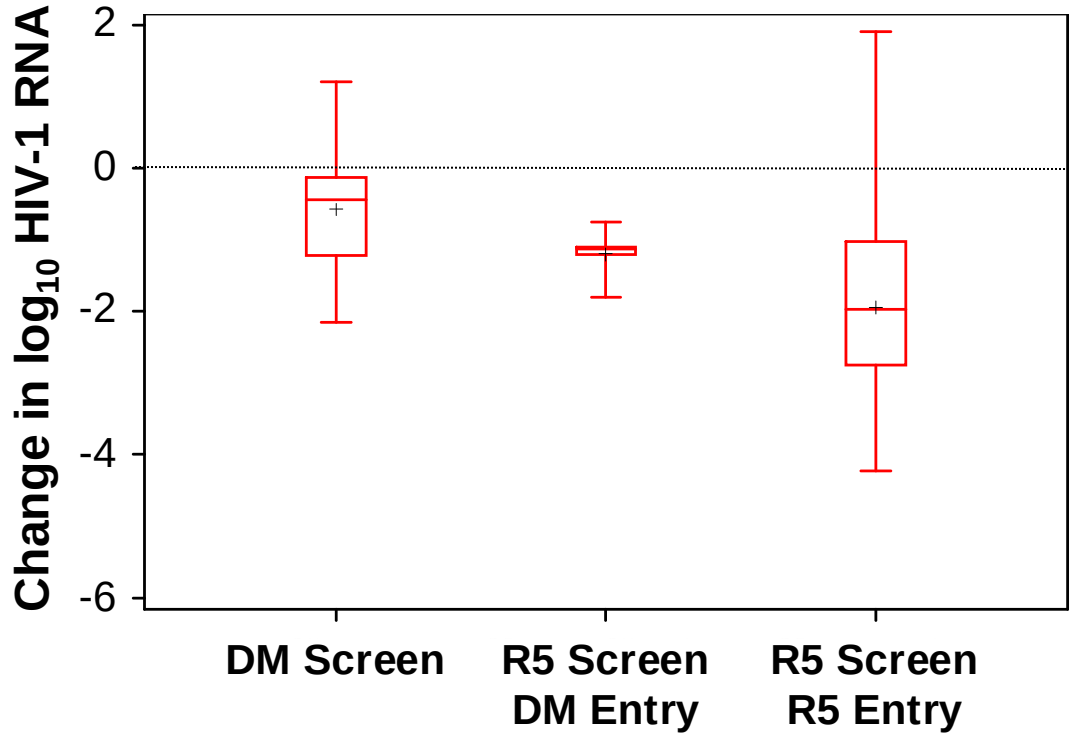
Standard Trofile				Enhanced Trofile		
n	Screen	Entry	on study CXCR4-use	Screen	n	%
12	R5	DM	yes*	DM	7/12	58
18	R5	R5	yes	DM	9/18	50
88	R5	R5	no	DM	9/86	10
118			*n=10			



- Enhanced Trofile reclassified 25 individuals with D/M virus at screen
- 15/25 were VCV recipients
- 12/15 had early emergence of CXCR4-using virus on study (week 2-8) by standard Trofile

Su et al. *J Infect Dis* 2009;200:1724-1728

Change in Viral Load among VCV Recipients at Week 24 by Coreceptor Tropism (Enhanced Trofile)



n	14	5	58
Mean	-0.57	-1.20	-1.95
Adjusted p value*	0.0003	0.0911	Reference

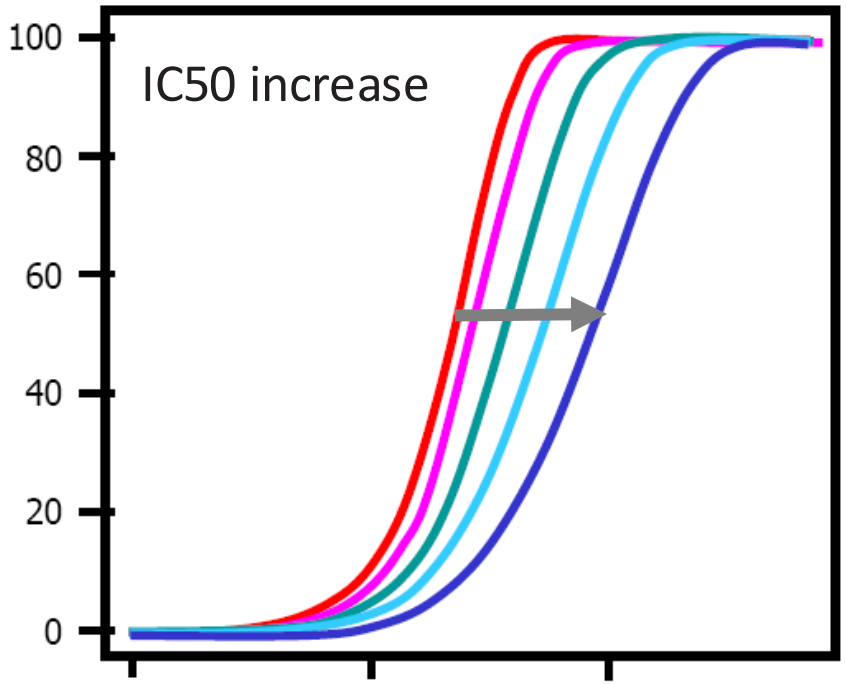
Greater viral load reductions were observed at day 14 and week 24 in subjects with R5 virus at screen and entry compared to D/M at screen by enhanced Trofile

*From a regression model adjusted for baseline log_{10} HIV-1 RNA and study stratification factors

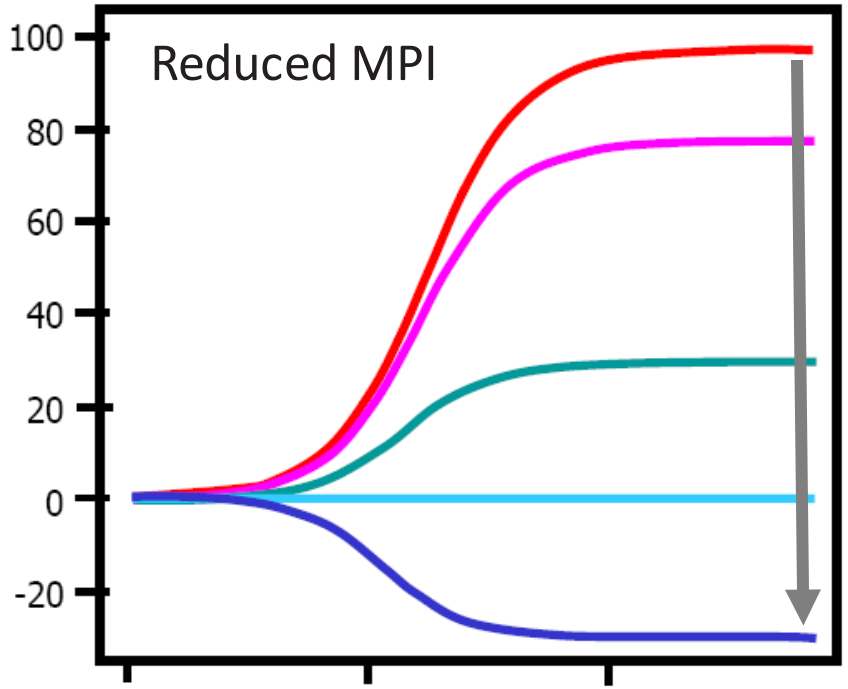
Su et al. *J Infect Dis* 2009;200:1724-1728

Two Profiles of Entry Inhibitor Resistance

Competitive inhibitors (e.g. enfuvirtide)



Non-competitive inhibitors (e.g. maraviroc)

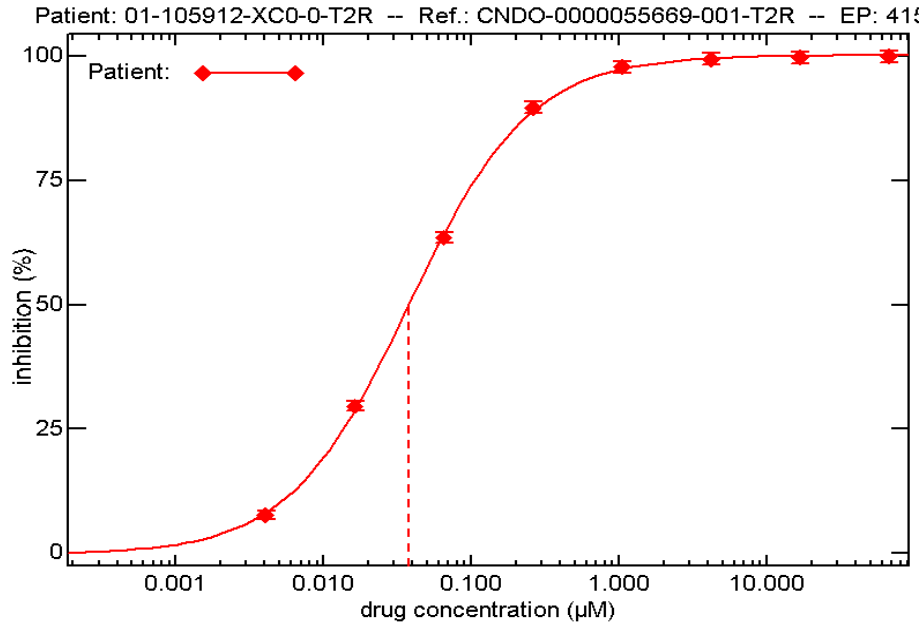


Drug concentration →

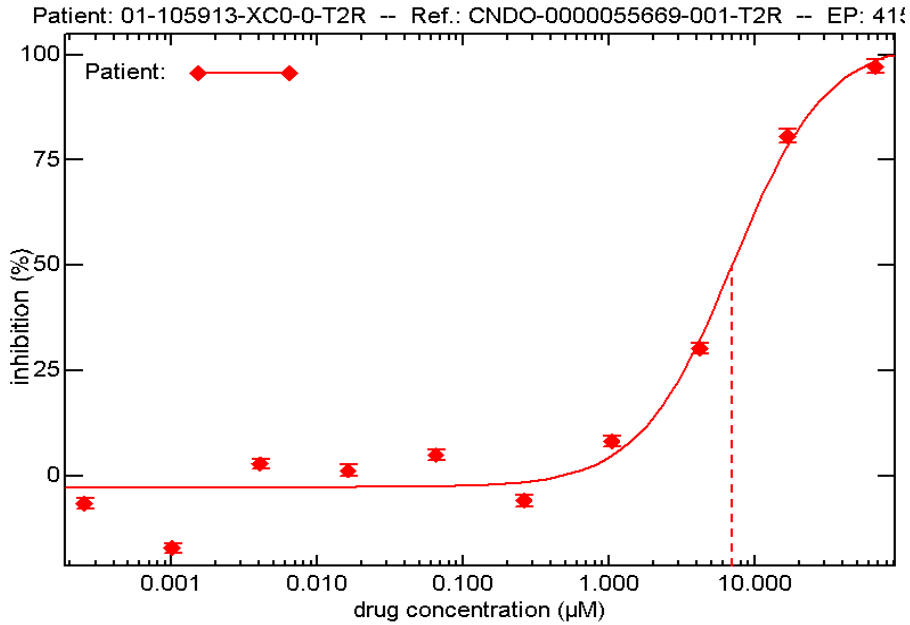
C. Petropoulos et al., DRW (2004)

TORO trial: enfuvirtide resistance

baseline



week 16



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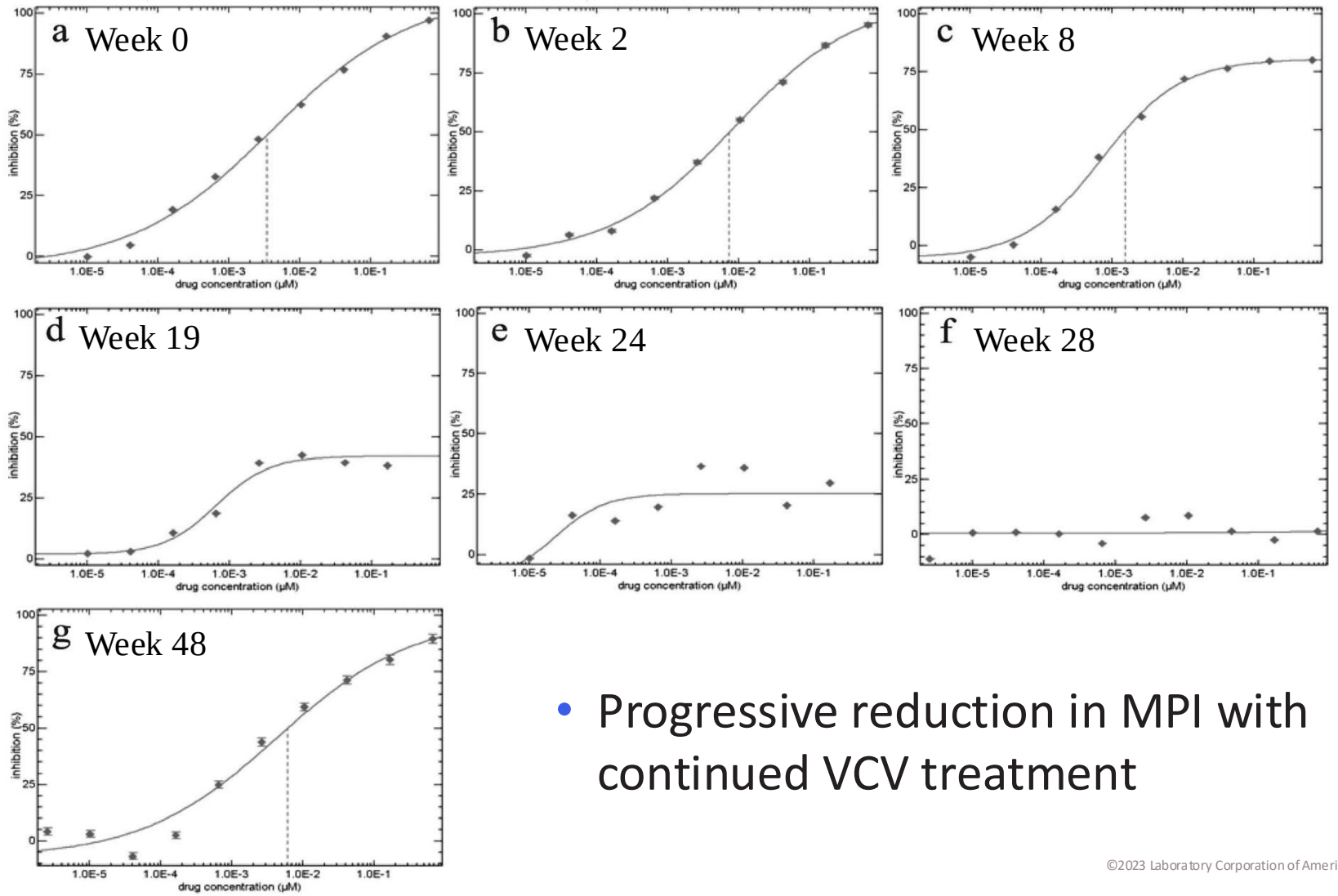
Evolution of Vicriviroc Resistance

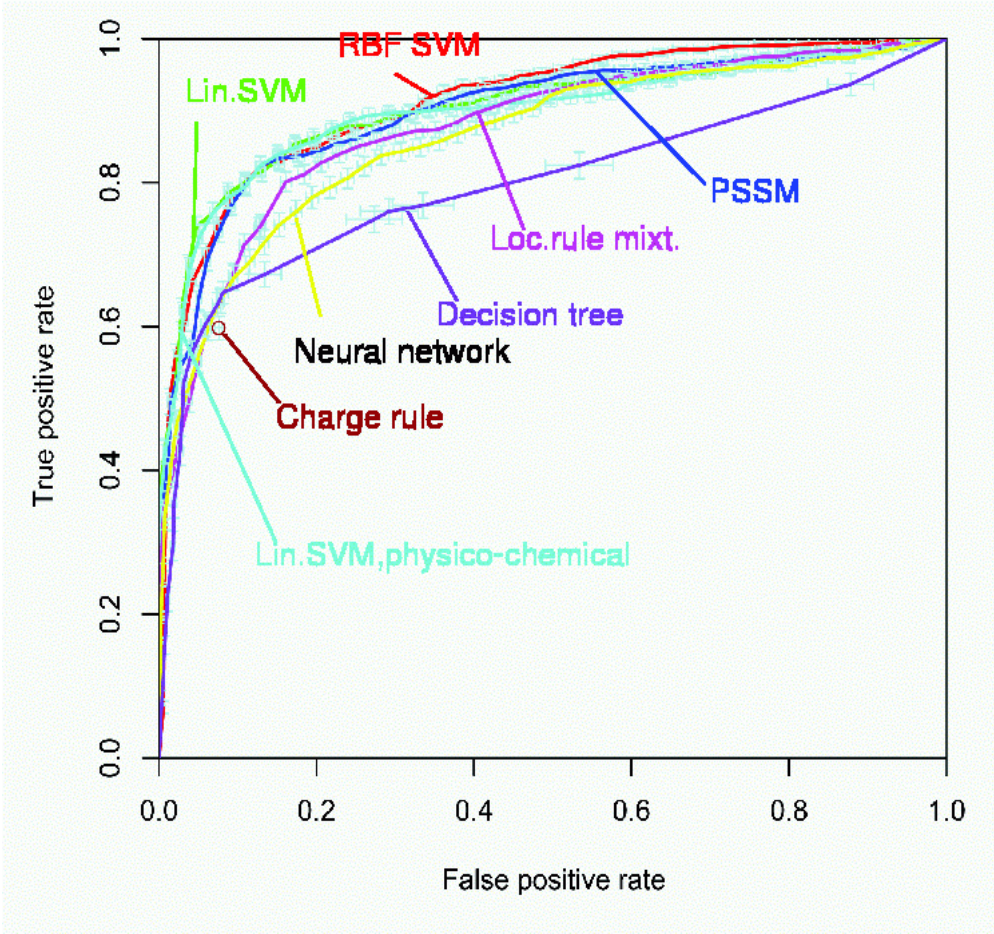


- Progressive reduction in MPI with continued VCV treatment

Envelope complexity - challenges for genotypic assay development

- The sequence diversity of HIV *env*, within and between individuals, presents challenges for the genotypic prediction of tropism
- The V3 loop is a primary determinant of HIV coreceptor tropism, however disparate discontinuous sequences in gp120 and gp41 can also influence tropism, limiting the sensitivity of genotypic algorithms
- When compared to phenotyping, genotypic methods based on V3 sequence may have high specificity (~90%) but low sensitivity (~50-75%) for predicting CXCR4-using virus

Genotypic prediction of CXCR4 use with different methods



https://coreceptor.geno2pheno.org/index.php

Coreceptor use and V3 sequences of envelope clones from 7 transmitted CXCR4-using viruses

- Dual tropic clones with low level CXCR4 use (Dual-R) are more difficult to predict with genotypic algorithms compared to those with efficient CXCR4-use (Dual-X)

		Infectivity measured by luciferase activity			Predictions			V3 sequence analysis	
Subject	No. of clones	R5 RLU (mediam)	X4 RLU (median)	Tropism (Trofile)	11KR/25KR	PSSM	Charge	PNGS	V3 amino acid sequences
1	11	174,105	769	dual-R	R5	R5	4	1	CTRPNNNTRK**S**IHMGPGKAFYATG**E**IIGDIRKAHC
	2	120,891	59	R5	R5	R5	4	1	.....
	1	83,223	50	R5	R5	R5	4	1	.....V.....
	1	164,877	461	dual-R	R5	R5	4	1	.....R.....
2	10	374986	4593	dual-R	R5	R5	4	1	CTRPNNNTRK**G**IHMGPGRVFYTTG**E**IIGDIRKAHC
	1	305047	18029	dual-R	R5	R5	5	1	.....R.....
	1	104,486	4,637	dual-R	X4	R5	6	1	.....K.....
	1	123,164	2,484	dual-R	R5	R5	4	1	.I.....
	1	164,741	3,654	dual-R	R5	R5	4	1	.....V.....
	2	240,359	677	dual-R	R5	R5	4	1	.....A...V.....
3	5	1,082,926	74	R5	R5	R5	4	1	CTRPGNNTRR**S**ITMGPGRAFYTTG**E**IIGDIRKAHC
	3	1,278,284	1,426	dual-R	R5	R5	4	1	.....
	5	8,862	349,224	dual-X	R5	R5	7	1	.....H..-H.R....KN.....
	1	11,893	27,700	dual-X	R5	R5	6	1	..G.....H..-H.R....KN.....
	1	71	328,864	X4	R5	X4	7	1	.....S...G.LV.-T.R....RN.....
4	13	529,308	759,363	dual-X	R5	R5	5	1	CTRPNNNTRK**G**IVIGPGRSFYAAR**S**IIGDIRQAHC
5	14	29,245	208,732	dual-X	X4	X4	4	1	CTRPNNNTIK**G**IRIGPGRAIYATE**K**IVGDIRQAHC
	1	106,948	135,564	dual-X	X4	X4	4	1	.....V.....
6	13	5,930	313,126	dual-X	X4	X4	6	0	CTRPNNNIRR**R**IHIGPGRAFYAT**D**ITGSIRRAYC
	1	5.294	207,153	dual-X	X4	X4	5	0	.....G.....
7	10	86	770,172	X4	X4	X4	5	0	CTRPNEYRTR**R**IHIGPGRAFVTTK**S**ITGDIRQAYC
	4	252	1,149,581	dual-X	X4	X4	5	0	.....
	1	82	454,024	X4	X4	X4	5	0	.....D.....

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DHHS guidelines - coreceptor tropism assays

- A co-receptor tropism assay should be performed whenever the use of a CCR5 co-receptor antagonist is being considered **(AI)**.
- Co-receptor tropism testing is recommended for patients who exhibit virologic failure on a CCR5 antagonist **(BIII)**.
- A phenotypic tropism assay is preferred to determine HIV-1 co-receptor usage **(AI)**.
  - Genotypic tropism assays may not be sufficiently robust to completely rule out the presence of an X4 or D/M variant; therefore, the Panel preferentially recommends phenotypic testing.
- A genotypic tropism assay should be considered as an alternative test to predict HIV-1 co-receptor usage **(BII)**.
- A proviral DNA tropism assay can be utilized for patients with undetectable HIV-1 RNA when a CCR5 antagonist is considered for use in a new regimen (e.g., as part of a regimen switch or simplification) **(BII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Weak*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Clinical Info HIV.gov. Updated/reviewed 2018

Partnering for international commercialization of a coreceptor tropism assay

- Pfizer partnered with Monogram throughout the clinical development of MVC through to approval and commercialization
- Trofile assay was used for clinical trial screening
- Evaluated different approaches to assess coreceptor tropism and assessed correlates of treatment failure (minor variants, plateaus)
- Collaborated on the reanalysis of MERIT with data from the enhanced sensitivity Trofile assay
- Partnered to facilitate international EAP, training of Medical Affairs, MSL, commercial teams etc
- Partnered to facilitate international access of Trofile assay upon MVC approval/availability (EU, N&S America)
  - Sponsored testing program initially available for no cost Ex-US access to Trofile

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Barriers to CCR5 antagonist uptake

- Subset of individuals eligible for treatment
  - From initial studies, approximately 50-60% of treatment-experienced individuals with ongoing viral replication and antiretroviral resistance had R5-tropic virus
- Requirement of selection assay with associated cost and TAT
- BID dosing regimen (MVC)
- Timing
  - MVC approval coincided with raltegravir approval; favorable properties - QD dosing, tolerability, no selection assay
  - VCV phase 3 participants had access to new drugs for OBT to control HIV (ralegravir, darunavir, etravirine)
- Selection assays originally for viremic individuals only (VL ≥1000 copies/mL)

Adapt assay to treatment paradigms – viremic (RNA) -> suppressed (DNA)

- Trofile is the gold standard for determining tropism in individuals with VLs greater than or equal to 1,000 copies/mL
- The ability to switch to or incorporate maraviroc into a suppressive treatment regimen had been precluded by the VL requirement
- Trofile DNA was developed to enable tropism determination in individuals whose virus is undetectable
- HIV DNA is isolated from infected cells in a whole blood sample
- Env sequences are amplified from cell-associated HIV DNA and incorporated into a test vector
- Assay sensitivity is determined by the number of copies of HIV DNA in a sample; most have less that 100 copies/test aliquot

trofile DNA
CO-RECEPTOR TROPISM ASSAY

biosciences
monogram

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Patient Name:	DOB	Patient ID/Medical Record #	Gender	Monogram Accession # 09-177165
Date Collected	Date Received	Date Reported	Mode	Report Status
Referring Physician			Reference Lab ID/Order #	
Comments:			HIV-1 Envelope Subtype: B	

Tropotype Result

R5 D/M X4

Dual/Mixed virus population can use CXCR4 and/or CCR5 co-receptors to enter the CD4+ cell.

D/M

ABOUT TROPISM

TROFILE® DNA–A NEW TROPISM ASSAY FROM MONOGRAM BIOSCIENCES.

Trofile DNA meets the US standards for technical validation as established by the Clinical Laboratory Improvement Amendments. Trofile DNA is a single cycle pseudovirion based tropism assay that uses the complete gp160 coding region of HIV-1 to evaluate tropism. Instead of using HIV-1 RNA isolated from patient plasma, Trofile DNA uses cell associated viral DNA taken from whole blood cells infected with HIV. HIV-1 envelopes encoded by the viral DNA are tested in a cell-based viral infectivity assay in order to determine which co-receptor the HIV-1 virus population is capable of using: CCR5, CXCR4, or both, known as D/M (dual/mixed).

TROFILE DNA VIRAL CLASSIFICATION

Co-receptor tropism is defined as an interaction of a virus with a specific co-receptor on the target cell. To gain entry into CD4+ cells, HIV must bind to the cell surface CD4 receptor and to one of two co-receptors, CCR5 or CXCR4. Trofile DNA uses the complete gp160 coding region of the HIV-1 envelope protein ensuring that all of the determinants of tropism tested.

CCR5 Tropic (R5) HIV-1:
Virus uses CCR5 to enter CD4+ cells.

CXCR4 Tropic (X4) HIV-1:
Virus uses CXCR4 to enter CD4+ cells.

DUAL/MIXED Tropic (D/M) HIV-1:
Dual-tropic viruses can use either CXCR4 or CCR5 to enter CD4+ cells. Mixed-tropic populations contain viruses with 2 or more tropisms.

Nonreportable:
Co-receptor tropism could not be determined. Common causes of nonreportable results are reduced viral fitness or compromised sample handling. Please note that Trofile DNA sample collection and handling instructions differ from Trofile and other Monogram assays.

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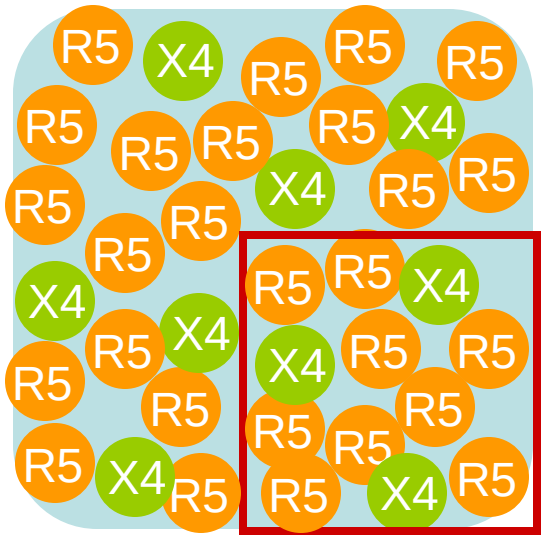
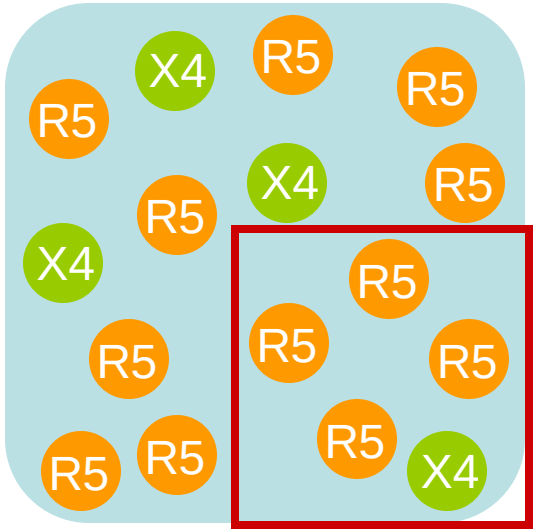
Sampling limitations

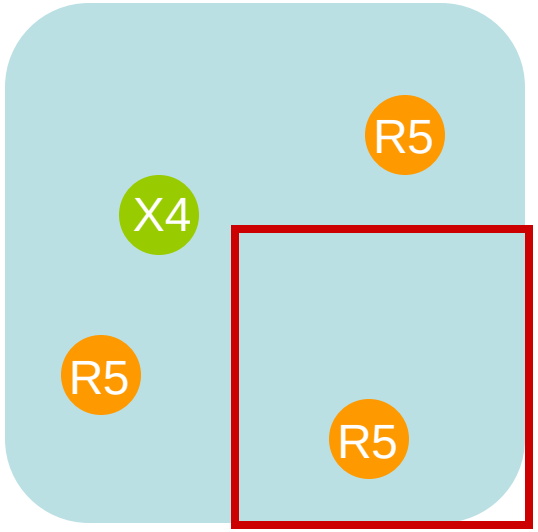
- Conventional assays based on sampling of plasma vRNA have a minimum viral load requirement that assures adequate variant representation
- Newer assays based on sampling of cell-associated vDNA are more vulnerable to sampling bias due to limitations in sample size



R5 = 75% of total
X4 = 25%
R5 = 75% of sample
X4 = 25%



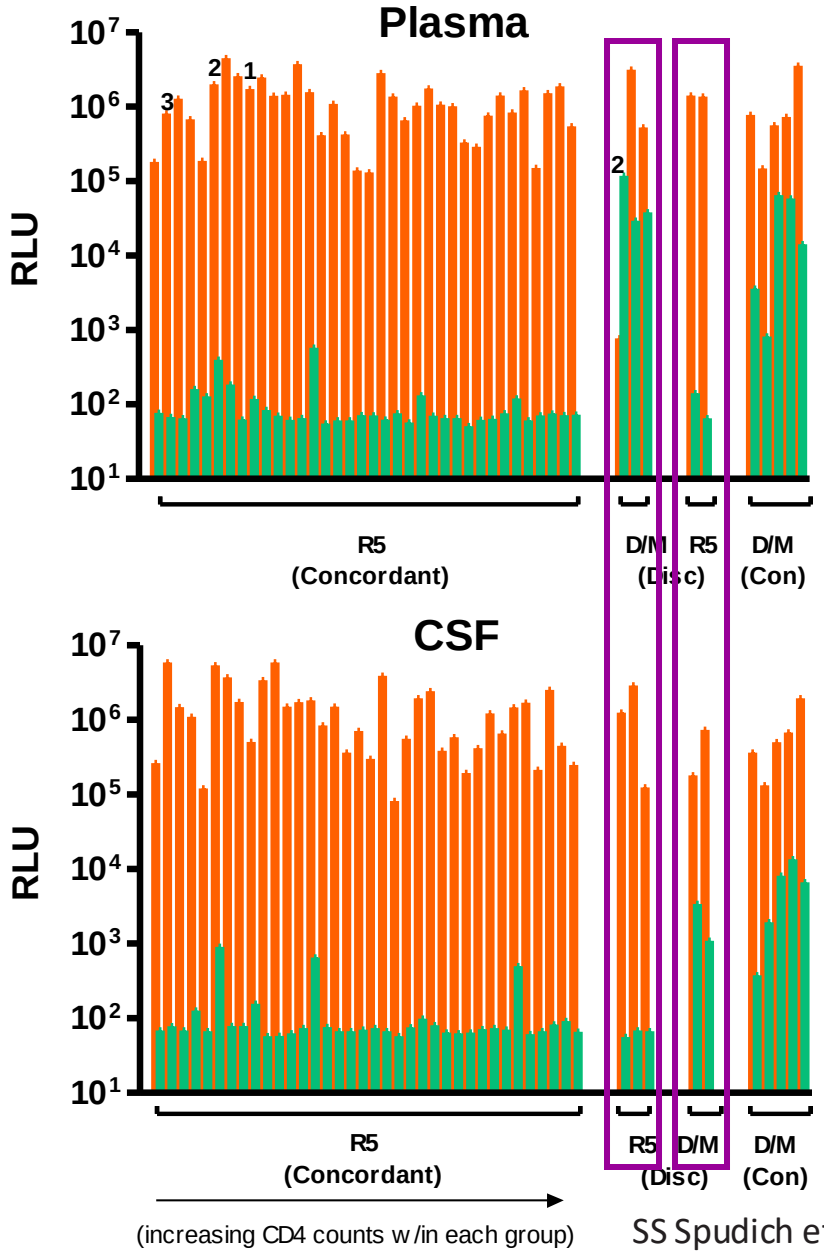
R5 = 75% of total
X4 = 25%
R5 = 80% of sample
X4 = 20%



R5 = 75% of total
X4 = 25%
R5 = 100% of sample
X4 = 0%

The tropism of virus sampled from different compartments can differ

-- CCR5 infectivity
-- CXCR4 infectivity



Tropism evaluated in 46 paired CSF and plasma samples

R5 Plasma: R5 CSF (36: 78.3%)

D/M Plasma: D/M CSF (5: 10.9%)

D/M Plasma: R5 CSF (3: 6.5%)

R5 Plasma: D/M CSF (2: 4.3%)

89.2% Concordant (41/46)

10.8% Discordant (5/46)

SS Spudich et al., J Inf Dis (2005)

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Lessons from CCR5 antagonists

- Screening assay required for optimal efficacy of CCR5 antagonists
- Collaborations between pharma, academic and diagnostic partners facilitated optimization of coreceptor tropism assay sensitivity to improve clinical utility of CCR5 antagonists
- Minor populations of CXCR4-using variants and reduced maximal percent inhibition can be associated with treatment failure. Potential for compartment tropism differences
- Envelope complexity presents challenges for genotypic assays
- Benefits from pharma-diagnostic partnership throughout drug/assay development and commercialization (e.g. reanalysis with enhanced sensitivity assay supported naïve indication for MVC without additional clinical trial)
- Minimize barriers to drug uptake – facilitate accredited assay access and coverage. US and EU solution may not be the same
- Timing – treatment needs to be a viable competitive option relative to others

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