HIV Virologic Failure

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July 17, 2019

Objectives

- *Demonstrate resistance testing through interactive case vignettes*
- *Describe resistance; how it develops and why it is important*
- *Outline how resistance is determined; testing, reporting and major mutations*
- *Discuss resistance testing interpretation*
- *Summarize virologic response definitions and when to perform resistance testing*

https://www.clcchurch.org/lets-go-straighter/

Case 1

45 yo TGF transferring care; diagnosed with HIV 7 years ago

- **She is unaware of what ARVs she has "been on" in the past**
- **Reports taking one pill a day**

Genotype demonstrates: L10I, K103N

HIV-VL: 120,000

CD4: 184 / 14%

CBC/CMP: WNL

What is a K103N?

K 103 N in Reverse Transcriptase (RT)

103 refers to amino acid position 103 in RT

K (Lysine) is the wild type amino acid

N (Asparagine) is the mutant amino acid

http://clipartlook.com/img-119485.html

What should we do at this time?

A. Start Azithromycin, Bactrim DS & Atripla™
B. Start Bactrim DS & Complera™
C. Start Triumeq™
D. Start Bactrim DS & Genvoya™
E. Start Bactrim DS & hold ARVs for now
F. Watch & Wait

Mutations: L10I, K103N
HIV-VL: 120,000
CD4: 184 / 14%

Non-nucleoside Reverse Transcriptase Inhibitors

efavirenz (EFV)	High-Level Resistance
etravirine (ETR)	Susceptible
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	Susceptible

NNRTI	EFV	ETR	NVP	RPV
K103N	60	0	60	0
Total	60	0	60	0

https://hivdb.stanford.edu/

Genotypic Score	
0 – 9	Susceptible
10 – 14	Potential Low-Level Resistance
15 – 29	Low-Level Resistance
30 – 59	Intermediate Resistance
≥ 60	High-Level Resistance

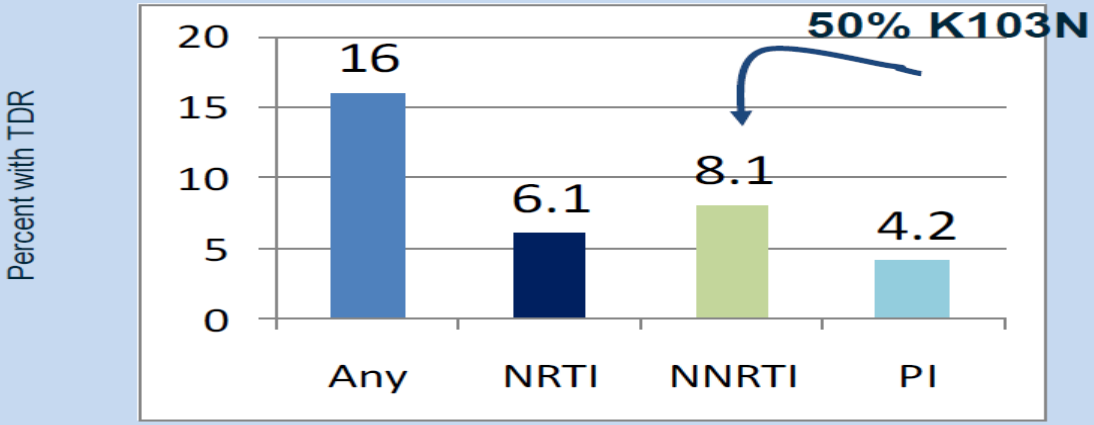
Genotype: genetic code of the sample virus is compared to the wild type
Phenotype: sample of HIV is grown with each ARV

http://hivdb.stanford.edu/
http://www.iasusa.org/resistance_mutations

Acknowledgment: Elizabeth Race, MD MPH

US Transmitted Drug Resistance: Newly Diagnosed

- 2007 CDC surveillance for TDR detected 16% of pts with new HIV diagnosis & mutations
  - Most common: NNRTI
  - 83% had single mutation



Primary Resistance in Young Pts: 55 recently infected pts (16-24 yo) from 15 US cities; approx. 50% AA; 25% Hisp.

Resistance	By Genotype	By Phenotype
Overall	18%	22%
NNRTI	15%	18%
PI	3.6%	5.5%
NRTI	4%	4%

Kim D, et al. 17th CROI; San Fran; February 16-19, 2010. Abst. 580; Viani R, et al. 13th CROI, Denver 2006; #21.

Genotype: genetic code of the sample virus is compared to the wild type
Phenotype: sample of HIV is grown with each ARV

Acknowledgment: Elizabeth Race, MD MPH

http://hivdb.stanford.edu/
http://www.iasusa.org/resistance_mutations

Records Arrive

Genotype:

- M184V, P225H

Nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	Low-Level Resistance
zidovudine (AZT)	Susceptible
stavudine (D4T)	Susceptible
didanosine (DDI)	Potential Low-Level Resistance
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	Susceptible

Non-nucleoside Reverse Transcriptase Inhibitors	
efavirenz (EFV)	High-Level Resistance
etravirine (ETR)	Susceptible
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	Susceptible

NRTI	ABC	AZT	D4T	DDI	FTC	3TC	TDF
M184V	15	-10	-10	10	60	60	-10
Total	15	-10	-10	10	60	60	-10

NNRTI	EFV	ETR	NVP	RPV
K103N	60	0	60	0
P225H	45	0	45	0
Total	105	0	105	0

Mutations: L10I, K103N, M184V, P225H

HIV-VL: 120,000

CD4: 184 / 14%

http://hivdb.stanford.edu/

What do we do now?

The next day additional records arrive
84V, 63P, 190Q, 65N

A. Refer or call someone
B. Bactrim DS & Symtuza™
C. Bactrim DS & Stribild™
D. Bactrim DS & Review Stanford HIV Database
E. Watch & Wait

Mutations: L10I, K103N, M184V, P225H, 84V, 63P, 190Q, 65N

HIV-VL: 120,000

CD4: 184 / 14%

Protease Inhibitors	
atazanavir/r (ATV/r)	High-Level Resistance
darunavir/r (DRV/r)	Low-Level Resistance
fosamprenavir/r (FPV/r)	High-Level Resistance
indinavir/r (IDV/r)	High-Level Resistance
lopinavir/r (LPV/r)	Intermediate Resistance
nelfinavir (NFV)	High-Level Resistance
saquinavir/r (SQV/r)	High-Level Resistance
tipranavir/r (TPV/r)	Intermediate Resistance

Nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	Intermediate Resistance
zidovudine (AZT)	Susceptible
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Non-nucleoside Reverse Transcriptase Inhibitors	
efavirenz (EFV)	High-Level Resistance
etravirine (ETR)	Intermediate Resistance
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	Intermediate Resistance

PI	ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	NFV	SQV/r	TPV/r
I84V	60	15	60	60	30	60	60	30
Total	60	15	60	60	30	60	60	30

NRTI	ABC	AZT	D4T	DDI	FTC	3TC	TDF
K65N	30	-10	30	30	15	15	30
M184V	15	-10	-10	10	60	60	-10
Total	45	-20	20	40	75	75	20

NNRTI	EFV	ETR	NVP	RPV
K103N	60	0	60	0
G190Q	60	45	60	45
P225H	45	0	45	0
Total	165	45	165	45

Mutations: L10I, K103N, M184V, P225H, 84V, 63P, 190Q, 65N

HIV-VL: 120,000

CD4: 184 / 14%

http://hivdb.stanford.edu/

Protease Inhibitors	
atazanavir/r (ATV/r)	High-Level Resistance
darunavir/r (DRV/r)	Low-Level Resistance
fosamprenavir/r (FPV/r)	High-Level Resistance
indina	
lopina	
nelfina	
saquin	
tipran	

Nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	Intermediate Resistance
zidovudine (AZT)	Susceptible
stavudine (D4T)	Low-Level Resistance
didanosine (DDI)	Intermediate Resistance
emtricitabine (FTC)	High-Level Resistance

Dosage Considerations

- There is evidence for low-level **DRV** resistance. If **DRV** is administered it should be used twice daily.

NRTI

- **M184V/I** cause high-level in vitro resistance to 3TC and FTC and low-level resistance to ddI and ABC. However, **M184V/I** are not contraindications to continued treatment with 3TC or FTC because they increase susceptibility to AZT, TDF and d4T and are associated with clinically significant reductions in HIV-1 replication.

NNRTI	EFV	ETR	NVP	RPV
K103N	60	0	60	0
G190Q	60	45	60	45
P225H	45	0	45	0
Total	165	45	165	45

Mutations: L10I, K103N, M184V, P225H, 84V, 63P, 190Q, 65N

HIV-VL: 120,000

CD4: 184 / 14%

http://hivdb.stanford.edu/

What is Resistance?

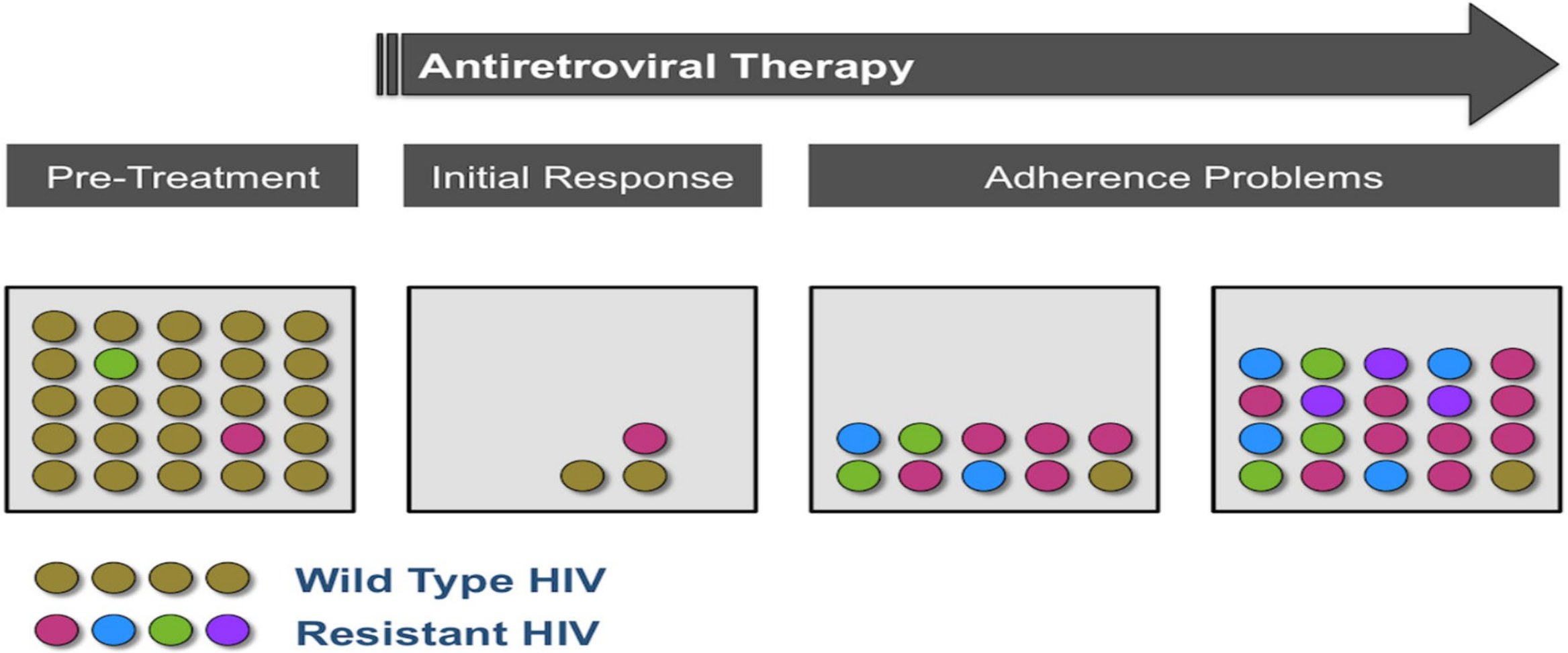


Figure 2 - HIV Resistance Basic Concepts
This graphic illustrates the basic concept that with suboptimal antiretroviral therapy, as may occur with poor adherence, drug-resistant strains of HIV have a selective advantage and can emerge to become the dominant circulating strains of HIV.

Illustration by David Spach, MD

https://www.hiv.uw.edu/go/antiretroviral-therapy/evaluation-management-virologic-failure/core-concept/all#hiv-drug-resistance-assays

Virologic Response Definitions on ART

Virologic Suppression: confirmed HIV RNA level below the LLOD of available assays

Virologic Failure: inability to achieve or maintain suppression of viral replication (<200 copies/mL)

Incomplete Virologic Response: 2 consecutive plasma HIV RNA levels ≥200 copies/mL after 24 weeks on an ARV regimen in a patient who has not yet had documented virologic suppression on this regimen. A patient's baseline HIV RNA level may affect the time course of response, and some regimens may take longer than others to suppress HIV RNA levels.

Virologic Rebound: Confirmed HIV RNA level ≥200 copies/mL after virologic suppression

Virologic Blip: After virologic suppression; an isolated detectable RNA level followed by suppression

Low-Level Viremia: Confirmed detectable HIV RNA level <200 copies/mL

LLOD: Lowest Level of Detection

https://www.hiv.uw.edu/
https://aidsinfo.nih.gov/

Reasons for Virologic Failure

Patient/Adherence-Related Factors

- Comorbidities: active substance abuse, mental health disorders, neurocognitive impairment
- Unstable housing and other psychosocial factors
- Missed clinic appointments
- Interruption of or intermittent access to ART
- Cost & affordability of ARVs
- Drug adverse effects
- High pill/bottle burden and/or dosing frequency

Antiretroviral Regimen-Related Factors

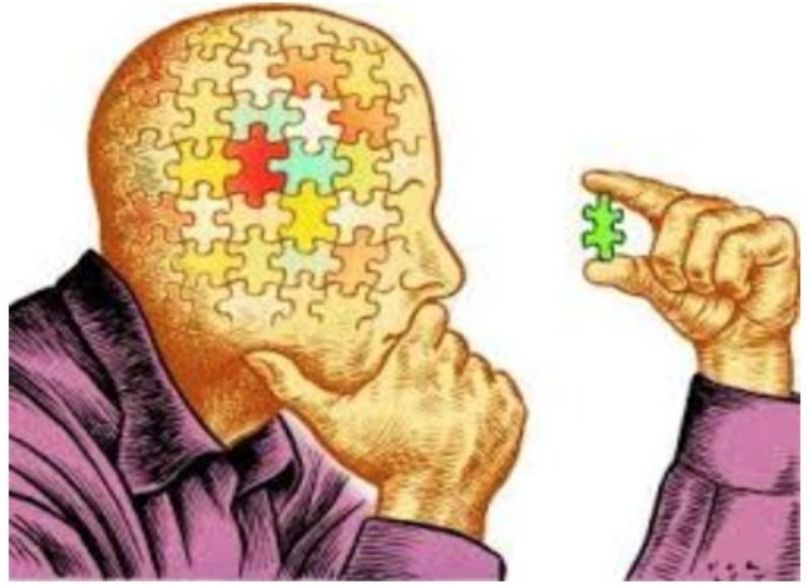
- Suboptimal pharmacokinetics; variable absorption, metabolism, or possible penetration into reservoirs
- Suboptimal virologic potency
- Low genetic barrier to resistance
- Reduced efficacy due to prior exposure to suboptimal regimens; mono- / dual –therapy or the sequential introduction of drugs
- Food requirements
- Adverse drug-drug interactions
- Prescription / Pharmacy errors

https://www.hiv.uw.edu/
https://aidsinfo.nih.gov/

Reasons for Virologic Failure

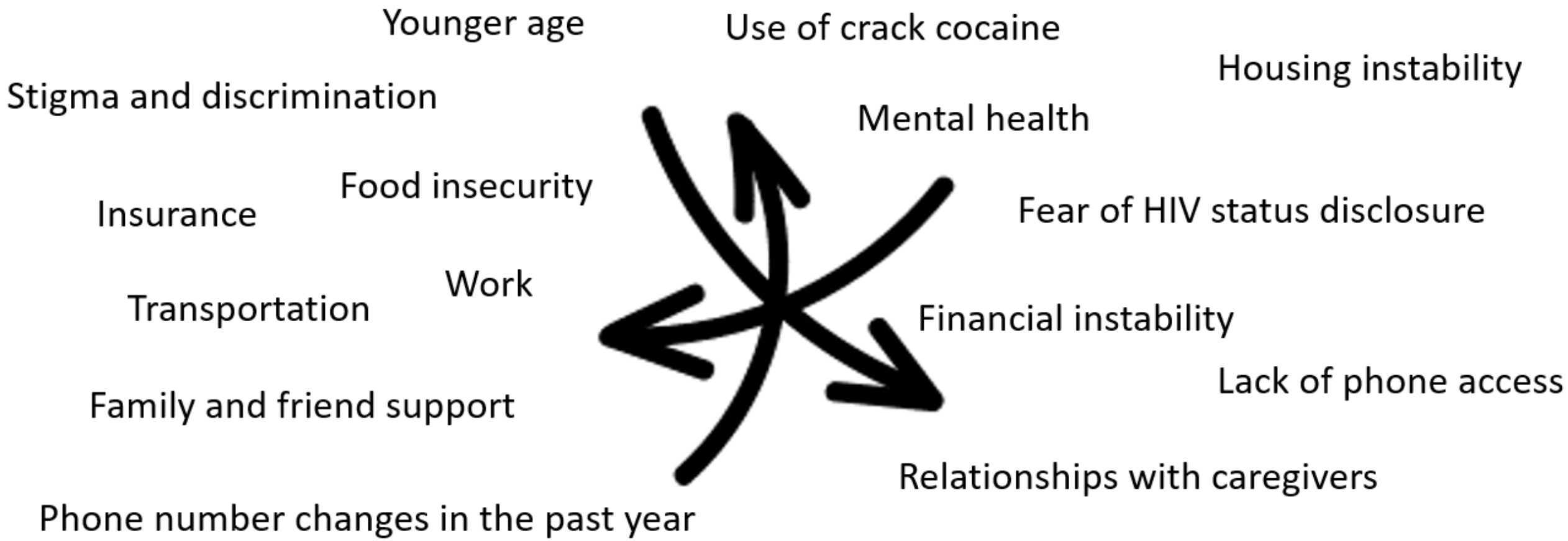
HIV-Related Factors

- Presence of transmitted or acquired drug-resistant virus documented by current or past resistance test results
- Prior treatment failure
- Innate resistance to ARVs due to viral tropism or the presence of HIV-2 infection/coinfection
- Higher pretreatment HIV RNA level
  - some regimens may be less effective at higher levels



http://www.chiromu.net/2017/07/01/the-multifactorial-approach-to-healthcare/
https://www.hiv.uw.edu/
https://aidsinfo.nih.gov/

Barriers to HIV Testing, Linkage, and Timely Initiation of HIV Prophylaxis or Treatment



Colasanti J, et al. *J Acquir Immune Defic Sydnr*. 2017;74(Suppl 2):S113–S120; Bohler R, et al. *Open Forum Infect Dis*. 2018;5(Suppl 1):S213; Hall BJ, et al. *AIDS Behav*. 2016;21(6):1755–1767; Remien RH, et al. *J Acquir Immune Defic Syndr*. 2015;69(0 1):S16–S24.

How is Resistance Determined?

Genotype

Tropism

Phenotype

Archive

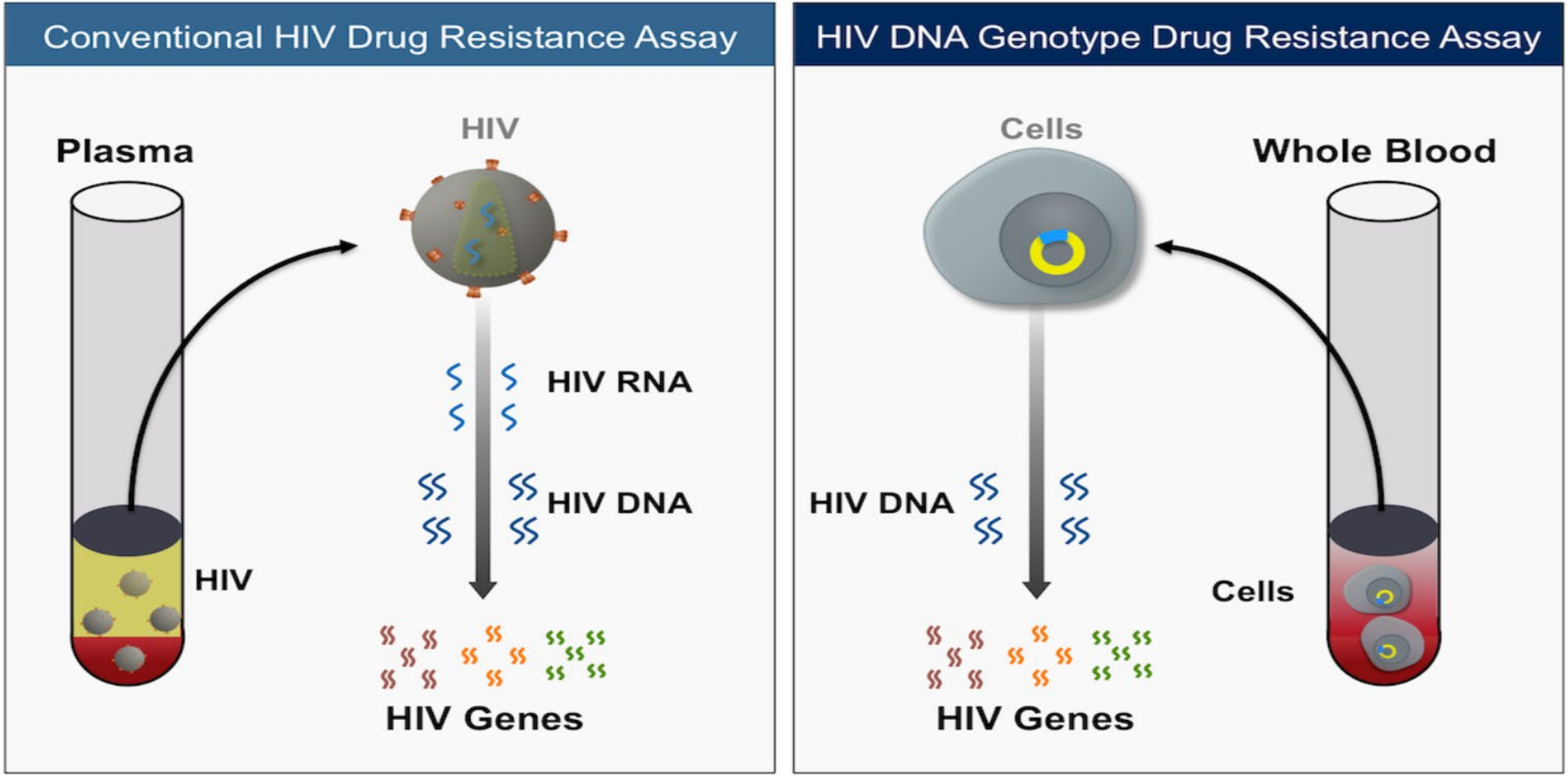


Figure 11 - HIV DNA Genotypic Drug Resistance Assay
In contrast to a conventional HIV drug resistance assay, which is performed on a patient plasma sample and typically requires HIV RNA levels of at least 500 copies/mL or more, a HIV DNA drug resistance assay in performed on whole blood and it detects proviral DNA that is incorporated into host DNA in cells infected with HIV. The HIV DNA resistance assay can be performed in patients who have undetectable plasma HIV RNA levels.

Illustration by David H. Spach, MD

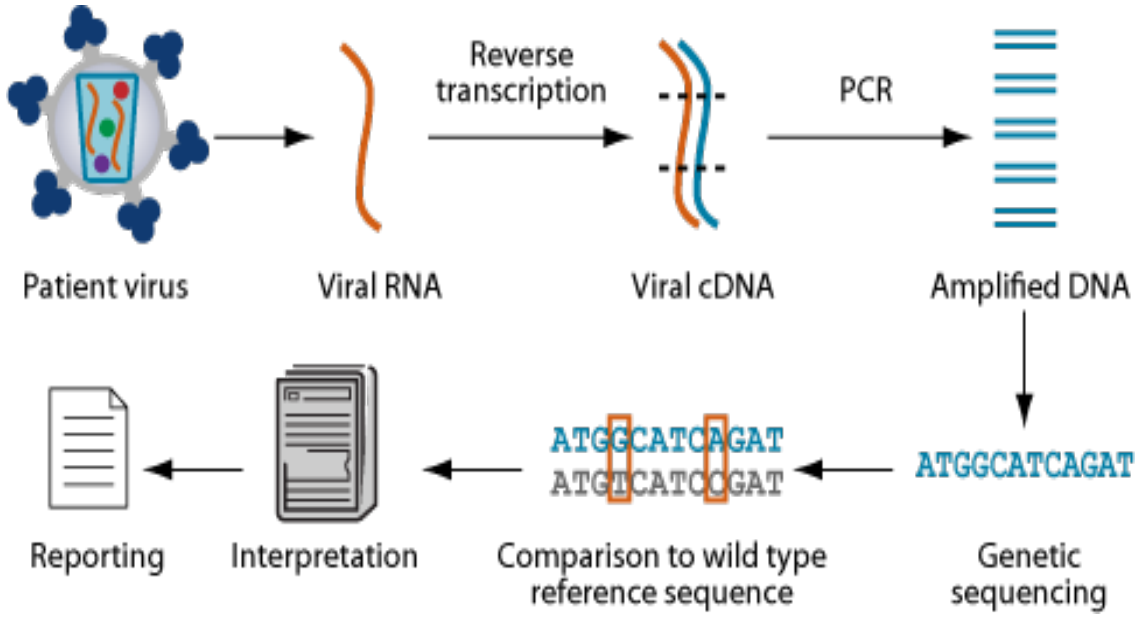
https://www.hiv.uw.edu/go/antiretroviral-therapy/evaluation-management-virologic-failure/core-concept/all#hiv-drug-resistance-assays

GenSure Prime®

Resistance test for 4 classes of HIV drugs

Identify pattern of HIV virus mutations from a sample of an individual's plasma.

Specific genetic patterns are associated with resistance to specific antiretrovirals.



GenoSure Archive: analyzes archived HIV-1 proviral DNA embedded in host cells during virus replication.

http://www.monogrambio.com/hiv-tests/genotypic-assays/genosure-prime

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

	Drug		GenoSure®MG	Assessment*		Comments
	Generic Name	**Brand Name**	**Drug Resistance Associated Mutations Detected**	**Drug**		
NRTI	**Abacavir**	Ziagen	None	ABC	Sensitive	
	Didanosine	Videx	None	ddI	Sensitive	
	Emtricitabine	Emtriva	None	FTC	Sensitive	
	Lamivudine	Epivir	None	3TC	Sensitive	
	Stavudine	Zerit	None	d4T	Sensitive	
	Tenofovir	Viread	None	TFV	Sensitive	
	Zidovudine	Retrovir	None	ZDV	Sensitive	
NNRTI	**Efavirenz**	Sustiva	K103N	EFV	Resistant	
	Etravirine	Intelence	None	ETR	Sensitive	
	Nevirapine	Viramune	K103N	NVP	Resistant	
	Rilpivirine	Edurant	K103N	RPV	Sensitive	
PI	**Atazanavir**	Reyataz	A71V	ATV	Sensitive	
		Reyataz / r*	A71V	ATV/r	Sensitive	
	Darunavir	Prezista / r*	V11I	DRV/r	Sensitive	
	Fosamprenavir	Lexiva / r*	V11I	AMP/r	Sensitive	
	Indinavir	Crixivan / r*	A71V	IDV/r	Sensitive	
	Lopinavir	Kaletra*	A71V	LPV/r	Sensitive	
	Nelfinavir	Viracept	A71V	NFV	Sensitive	
	Ritonavir	Norvir	A71V	RTV	Sensitive	
	Saquinavir	Invirase / r*	A71V	SQV/r	Sensitive	
	Tipranavir	Aptivus / r*	A71V	TPV/r	Sensitive	

Patient Name	DOB	Patient ID/Medical Record #	Gender	Monogram Accession #
Date Collected	Date Received	Date Reported	Mode	Report Status

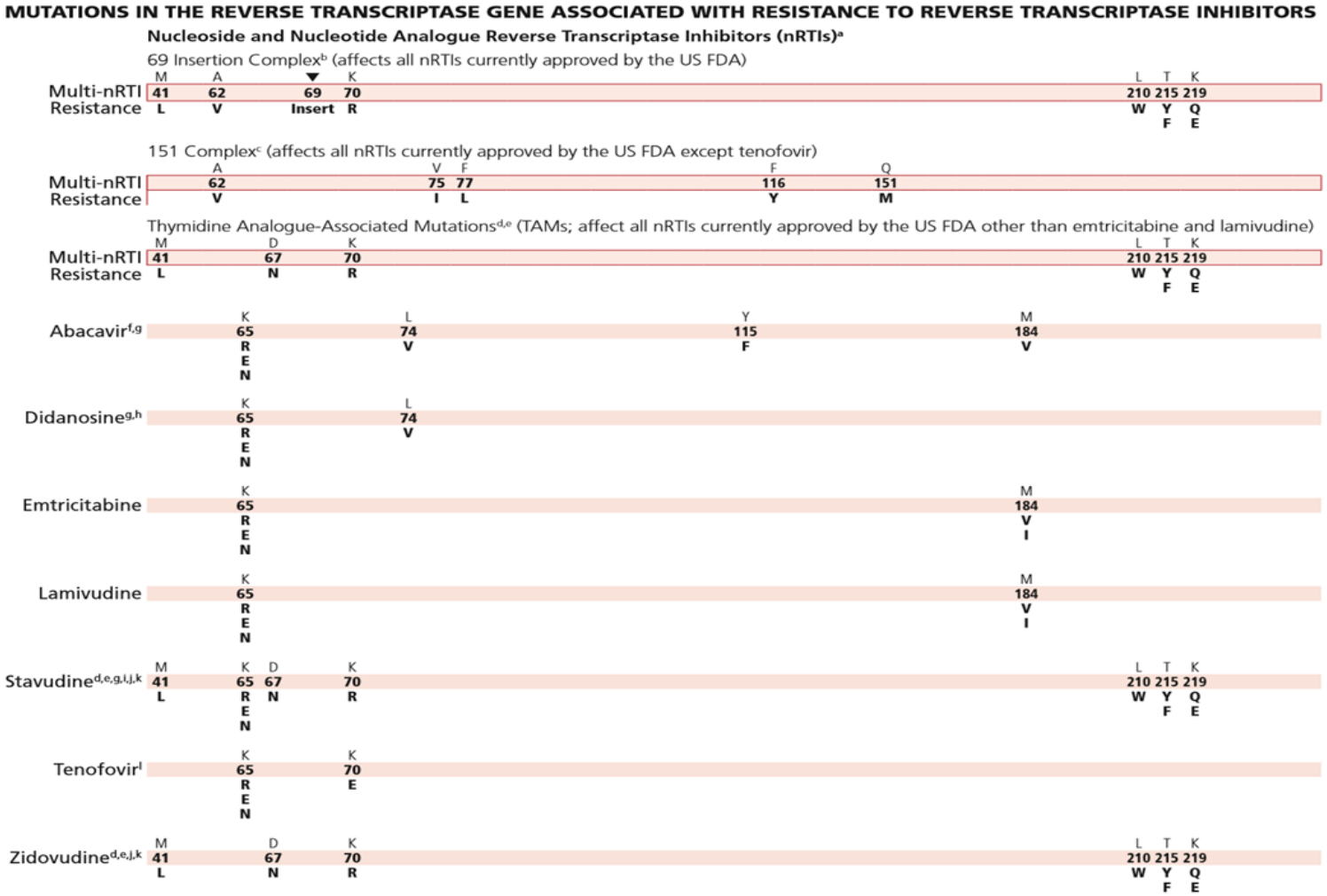
* Assessment of drug susceptibility is based upon detected mutations and interpreted using an advanced proprietary algorithm (version 16).
♯ Interpretation algorithms for ritonavir-boosted protease inhibitors appropriate for the following dosages: AMP/r 600mg/100mg BID; ATV/r 300mg/100mg QD; IDV/r 800mg/200mg BID; LPV/r 400mg/100mg BID; SQV/r 1000mg/100mg BID; TPV/r 500mg/200mg BID; and DRV/r 600mg/100mg BID.
* **Mixtures** are indicated by amino acids separated by a slash. Deletions in the amino acid sequence are indicated by a ^ symbol.

Summary of Mutations Observed

RT K13R, Q102K, K103N, I142T, C162S, Q197E, R211K, A272S, V276I, R277K, V292I, E297V, I326V, A327V, Y339F, P345Q, M357I, K358R, T377V, V381I, T386I, A400T

PR V11I, I64V, K70R, A71V, I72E, V77I, I93L

Major Mutations



MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH RESISTANCE TO REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)[a]

69 Insertion Complex[b] (affects all nRTIs currently approved by the US FDA)

	M	A		K										L	T	K
Multi-nRTI Resistance	41	62		69	70									210	215	219
	L	V		Insert	R									W	Y	Q
															F	E

151 Complex[c] (affects all nRTIs currently approved by the US FDA except tenofovir)

	A			V	F					F		Q				
Multi-nRTI Resistance	62			75	77					116		151				
	V			I	L					Y		M				

Thymidine Analogue-Associated Mutations[d,e] (TAMs; affect all nRTIs currently approved by the US FDA other than emtricitabine and lamivudine)

	M		D	K										L	T	K
Multi-nRTI Resistance	41		67	70										210	215	219
	L		N	R										W	Y	Q
															F	E

	K			L			Y			M						
Abacavir[f,g]	65			74			115			184						
	R			V			F			V						
	E															
	N															

	K			L												
Didanosine[g,h]	65			74												
	R			V												
	E															
	N															

	K									M						
Emtricitabine	65									184						
	R									V						
	E									I						
	N															

	K									M						
Lamivudine	65									184						
	R									V						
	E									I						
	N															

	M	K	D		K									L	T	K
Stavudine[d,e,g,i,j,k]	41	65	67		70									210	215	219
	L	R	N		R									W	Y	Q
		E													F	E
		N														

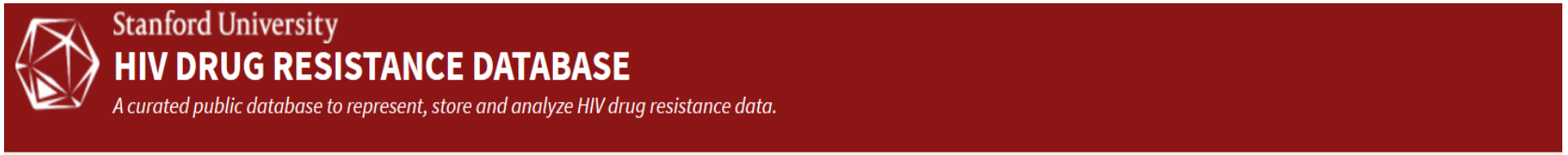
	K		K													
Tenofovir[l]	65		70													
	R		E													
	E															
	N															

	M		D	K										L	T	K
Zidovudine[d,e,j,k]	41		67	70										210	215	219
	L		N	R										W	Y	Q
															F	E

https://hivdb.stanford.edu/pages/download/resistanceMutations_handout.pdf

https://www.iasusa.org/sites/default/files/2017-drug-resistance-mutations-hiv-1-figure.pdf

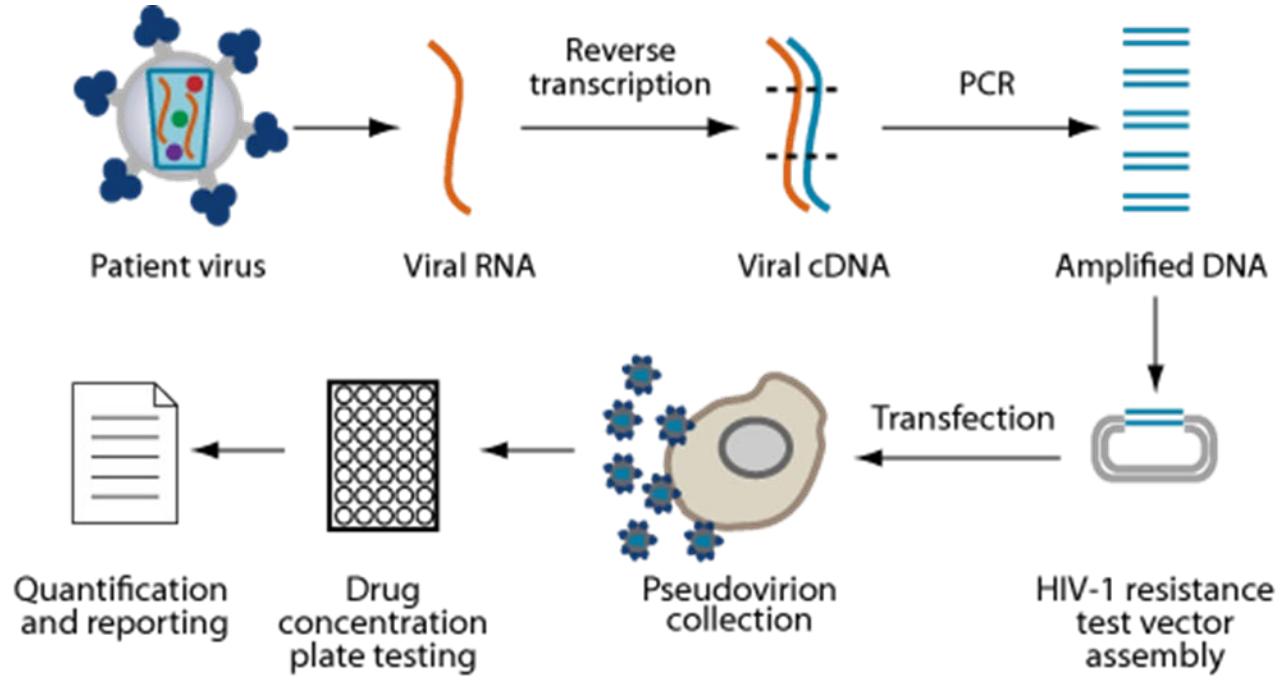
Major Mutations



https://hivdb.stanford.edu/pages/download/resistanceMutations_handout.pdf
https://www.iasusa.org/sites/default/files/2017-drug-resistance-mutations-hiv-1-figure.pdf

Phenotypic Assay

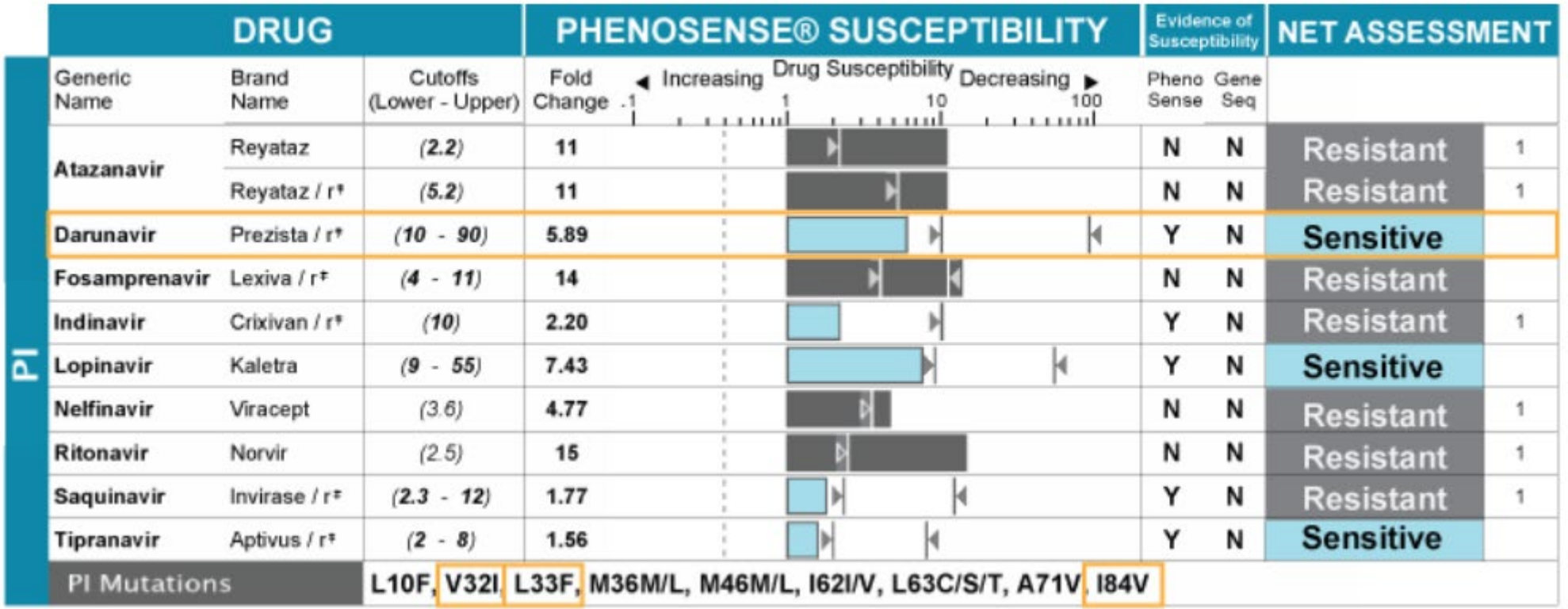
Performed by exposing a sample of HIV to all of the available ARV drugs



The activity of a patient's HIV in the presence of the ARV drugs is compared to the activity of a control strain of HIV that is known to be susceptible to a specific drug.

http://www.monogrambio.com/hiv-tests/phenotypic-assays

PhenoSense®



	DRUG			PHENOSENSE® SUSCEPTIBILITY			Evidence of Susceptibility		NET ASSESSMENT	
	Generic Name	Brand Name	Cutoffs (Lower - Upper)	Fold Change	◄ Increasing Drug Susceptibility Decreasing ► .1 1 10 100		Pheno Sense	Gene Seq		
PI	Atazanavir	Reyataz	(2.2)	11			N	N	Resistant	1
		Reyataz / r‡	(5.2)	11			N	N	Resistant	1
	Darunavir	Prezista / r‡	(10 - 90)	5.89			Y	N	Sensitive	
	Fosamprenavir	Lexiva / r‡	(4 - 11)	14			N	N	Resistant	
	Indinavir	Crixivan / r‡	(10)	2.20			Y	N	Resistant	1
	Lopinavir	Kaletra	(9 - 55)	7.43			Y	N	Sensitive	
	Nelfinavir	Viracept	(3.6)	4.77			N	N	Resistant	1
	Ritonavir	Norvir	(2.5)	15			N	N	Resistant	1
	Saquinavir	Invirase / r‡	(2.3 - 12)	1.77			Y	N	Resistant	1
	Tipranavir	Aptivus / r‡	(2 - 8)	1.56			Y	N	Sensitive	
	PI Mutations		L10F, V32I, L33F, M36M/L, M46M/L, I62I/V, L63C/S/T, A71V, I84V							

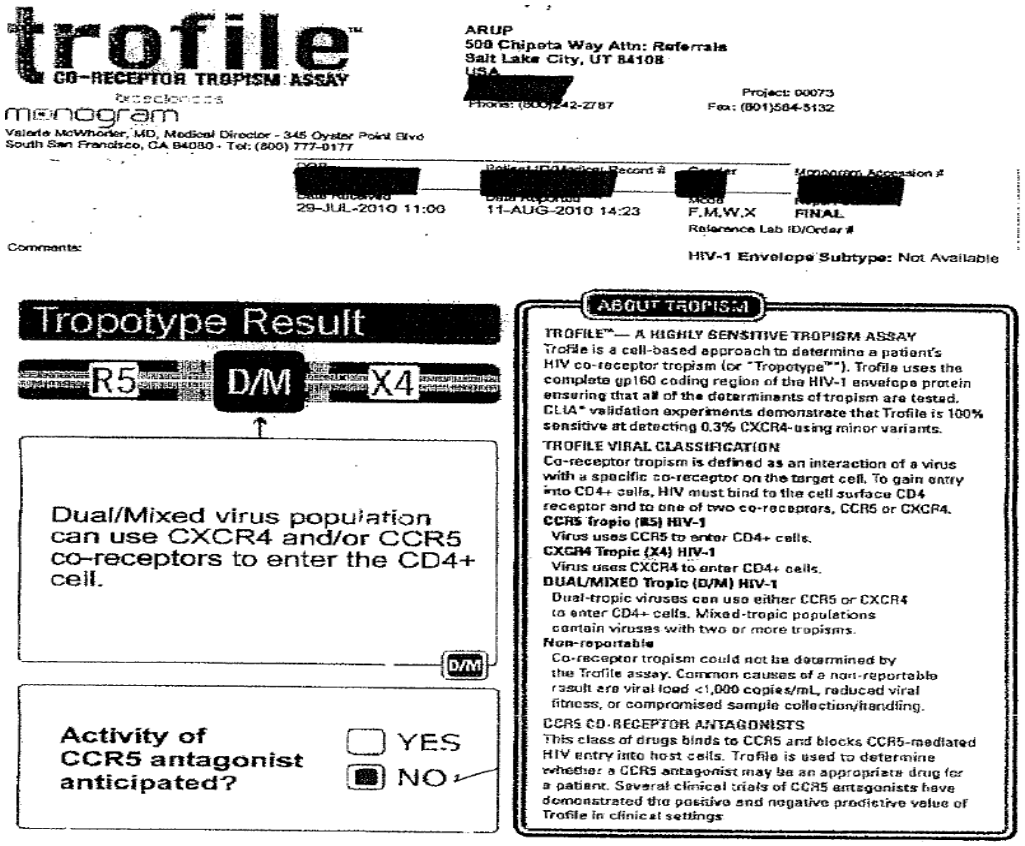
https://www.monogrambio.com/hiv-tests/combined-phenotype-genotype-assays/phenosense-gt

Tropism

Assay for HIV-1 co-receptor usage

Performed if a CCR5 antagonist is being considered

Re-Test with virologic failure on a CCR5 antagonist



trofile™
CO-RECEPTOR TROPISM ASSAY
monogram Biosciences

ARUP
500 Chipeta Way Attn: Referrals
Salt Lake City, UT 84108
USA
[redacted]
Project: 00073
Fax: (801)584-5132

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

DOB	Patient ID/Medical Record #	Gender	Monogram Accession #
[redacted]	[redacted]	[redacted]	[redacted]
Date Collected	Date Received	Mode	Report Status
29-JUL-2010 11:00	11-AUG-2010 14:23	F,M,W,X	FINAL

Comments:

Reference Lab ID/Order #

HIV-1 Envelope Subtype: Not Available

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

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.

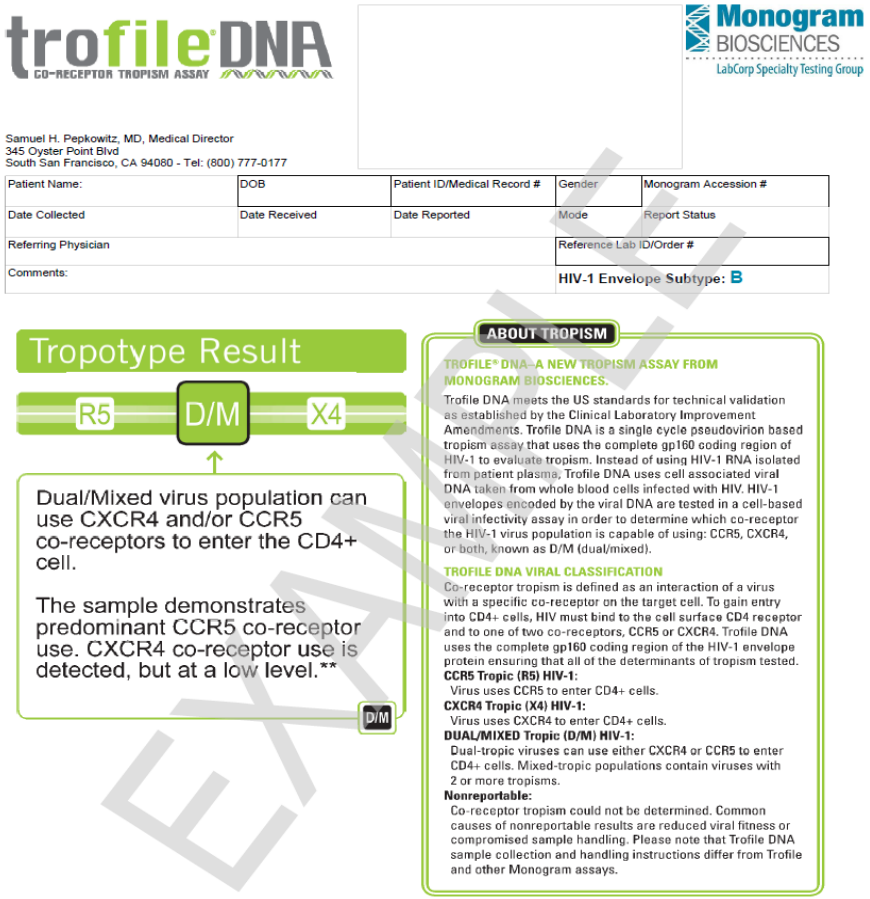
CCR5 Tropic (R5) HIV-1
Virus uses CCR5 to enter CD4+ cells.

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.



trofile DNA
CO-RECEPTOR TROPISM ASSAY

Monogram BIOSCIENCES
LabCorp Specialty Testing Group

Samuel H. Pepkowitz, MD, Medical Director
345 Oyster Point Blvd
South San Francisco, CA 94080 - Tel: (800) 777-0177

Patient Name:	DOB	Patient ID/Medical Record #	Gender	Monogram Accession #
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.

The sample demonstrates predominant CCR5 co-receptor use. CXCR4 co-receptor use is detected, but at a low level.**

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.

EXAMPLE

Limitations: genotypic and phenotypic assays

- Both assays analyze the dominant circulating HIV strains
  - may fail to detect mutant strains that constitute a minority of the HIV population
- The failure to detect minority populations can occur in several scenarios:
  - as mutant populations emerge, they may exist in low numbers
  - if ARV discontinuation, wild-type virus tends to outgrow and obscure resistant virus;
  - ARV switch: selective drug pressure changes and resistant populations may diminish to a level below the threshold for detection on the resistance assay
  - absent or altered drug pressure, previously generated resistance mutations may exist archived at low levels but will re-emerge to confer resistance if the previously used antiretroviral agent is re-introduced
- Thus, resistance tests provide the most accurate information if they are performed while the on ART & HIV drug resistance tests most accurately reflect resistance to medications the patient is currently taking. The tests less reliably detect resistance to drugs taken in the past.

https://www.hiv.uw.edu/
https://aidsinfo.nih.gov/

Resistance Testing: When to Test?

Acute HIV Infection: Genotype Do not delay treatment while awaiting results	Determine if drug-resistant virus was transmitted Consider repeat testing if ARVs deferred – superinfection
ART-Naive with Chronic HIV	Transmitted baseline HIV resistance to at least 1 drug: 10-17%
Pregnancy	ART can be initiated prior to receiving test result
CCR5 antagonist consideration	Perform co-receptor tropism assay

https://aceclifehealthtrust.com/roll-resistance-tips-better-communication/

https://www.hiv.uw.edu/
https://aidsinfo.nih.gov/

Resistance Testing with Virologic Failure

- Recommended if on combination ART & HIV RNA levels >1,000 copies/mL
  - If HIV RNA levels >500 but <1,000 copies/mL, testing should still be considered
- Testing should be done while taking ART or within 4 weeks after ART discontinuation
  - If >4 weeks have elapsed, resistance testing may still be useful to guide therapy
  - Standard genotypic assay is generally preferred for patient's 1st or 2nd regimens
- **All prior & current resistance testing results should be reviewed & considered when designing a new regimen for a patient experiencing virologic failure**
- Adding phenotypic testing to genotypic testing is preferred with known or suspected complex drug-resistance patterns

https://www.hiv.uw.edu/
https://aidsinfo.nih.gov/

Suboptimal Viral Load Suppression Undetectable Viral Load or Low-Level Viremia

Drug-resistance testing is recommended in patients with suboptimal viral load suppression after initiation of ART

HIV-1 proviral DNA resistance assays may be useful with HIV RNA below the limit of detection or with low-level viremia, where a HIV RNA genotypic assay is unlikely to be successful

http://clipartbarn.com/thinking-clip-art_6405/

https://www.hiv.uw.edu/
https://aidsinfo.nih.gov/

2

- 38 yo AAM entering into care
  - He is unaware of what ARVs he has “been on” in the past
  - Reports taking several types of pills over the years with many SEs
  - Points to: AZT, CBV, TDF, Truvada, Kaletra, DTG, Descovy, Evotaz
- Archive genotype demonstrates:
  - 36I, 62V, 219Q, 138A, 179D, 190A, 318F, 101Q, 143C, 230R
- HIV-VL: 98,000
- CD4: 86 / 4.1%
- eGFR: 61

https://www.pinterest.com/pin/129337820527836565/

What should we do at this time?

A. Refer or call someone else
B. Start Azithromycin, Bactrim DS & Biktarvy™
C. Start Bactrim, Descovy™ & Evotaz™
D. Start Bactrim DS & review Stanford HIV DB
E. Start Bactrim & Watch & Wait

Archive genotype demonstrates:
36I, 62V, 219Q, 138A, 179D, 190A, 318F, 101Q, 143C, 230R

HIV-VL: 98,000

CD4: 86 / 4.1%

eGFR: 61

Mutations Review

Integrase Strand Transfer Inhibitors

bictegravir (BIC)	Low-Level Resistance
dolutegravir (DTG)	Intermediate Resistance
elvitegravir (EVG)	Intermediate Resistance
raltegravir (RAL)	High-Level Resistance

INSTI	BIC	DTG	EVG	RAL
Y143C	5	5	10	60
S230R	10	20	20	20
Y143C + S230R	5	5	5	0
Total	20	30	35	80

Dosage Considerations

- There is evidence for intermediate **DTG** resistance. If **DTG** is used, it should be administered twice daily.

https://hivdb.stanford.edu/

Chart Review: Records Obtained

CCC called: Descovy™ + Prezcobix™

HIV-VL decr. to 26,000

CD4: 132/6%

Review of all available (R) tests (archived):

36I, 62V, 63P/S, 65R, 184I/V, 219Q, 138A, 179D, 190A, 230L, 318F, 101Q, 103R, 143C, 230R, 74M, 151I

Repeat resistance testing without new mutations

https://nccc.ucsf.edu/

What should we do at this time?

A. Refer or call someone else
B. Start Azithromycin, Bactrim DS & Biktarvy™
C. Start Bactrim, Genvoya™ & Prezista™
D. Start Bactrim DS & review Stanford HIV DB
E. Start Bactrim & Watch & Wait

Mutations: 36I, 62V, 63P/S, 65R, 184I/V, 219Q, 138A, 179D, 190A, 230L, 318F, 101Q, 103R, 143C, 230R, 74M, 151I

HIV-VL: 26,000

CD4: 132 / 6%

eGFR: 61

https://hivdb.stanford.edu/

Genotypic Score	
0 – 9	Susceptible
10 – 14	Potential Low-Level Resistance
15 – 29	Low-Level Resistance
30 – 59	Intermediate Resistance
≥ 60	High-Level Resistance

https://hivdb.stanford.edu/

Integrase Strand Transfer Inhibitors

bictegravir (BIC)	Low-Level Resistance
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Y143C	5	5	10	60
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Total	20	30	35	80

Dosage Considerations

- There is evidence for intermediate **DTG** resistance. If **DTG** is used, it should be administered twice daily.

Descovy + Prezcobix: TDF (60), FTC (95), DRV (0) – monotherapy

Changed ARVs: AZT (-10: close monitoring), Prezcobix (0) + DTG (30: twice day)

Follow-up: HIV-VL: <40 and CD4: 201/12%. eGFR: 70, Hgb: 13.7

https://hivdb.stanford.edu/

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That which is not good for the bee-hive cannot be good for the bees.

Marcus Aurelius