HIV R&R:
REGIMENS AND RESISTANCE

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DISCLOSURE

- None!

OBJECTIVES

- Review goals and principles of HIV treatment
- Discuss the commonly utilized regimens for antiretroviral naïve patients
- Discuss antiretroviral resistance and implications on HIV treatment
- Review the monitoring parameters for HIV treatment

PRINCIPLES OF TREATMENT

- 3 full active antiretrovirals
- At least 2 classes of antiretrovirals represented
- Ideal Treatment
  - Effective
  - Simple to take
  - No drug interactions
  - Well tolerated
- Recommended for Everyone with HIV

GOALS OF TREATMENT

- Eradication?

- Primary goals:
  1. Reduce HIV-associated morbidity and prolong the duration and quality of survival
  2. Restore and preserve immunologic function
  3. Maximally and durably suppress plasma HIV viral load (VL <50 copies/ml)
  4. Prevent HIV transmission

ADHERENCE

- >95% adherence to achieve therapeutic goals
- 10% reduction in adherence = doubling of VL
- Result of non-adherence- RESISTANCE
- Reasons for poor adherence:

Knowledge/Understanding	Side Effects
Irregular schedules	Pill Fatigue
Memory	Access to meds/$$
Mental Health Issues	Illicit Drug Abuse
Issues swallowing	

FIRST-LINE THERAPIES
FOR TREATMENT-NAÏVE PATIENTS

AETC AIDS Education & Training Center Program

Brand Name	Generic Name	Classes Represented	Pill Burden
Biktarvy®	Bictegravir Tenofovir alafenamide (TAF) Emtricitabine	Integrase Inhibitor (INSTI) NRTI NRTI	1 pill Once a day
Triumeq®	Dolutegravir/ Abacavir/ Lamivudine	INSTI NRTI NRTI	1 pill Once a day
Descovy® OR Truvada® PLUS Tivicay®	Tenofovir/ Emtricitabine Dolutegravir	NRTI NRTI INSTI	2 pills Once a day
Descovy® OR Truvada® PLUS Isentress®	Tenofovir/ Emtricitabine PLUS Raltegravir	NRTI NRTI INSTI	1 pill once a day 1 pill twice a day or 2 pills once a day

BIKTARVY®
BICTEGRAVIR / TENOFOVIR ALAFENAMIDE (TAF)/EMTRICITABINE

- Integrase inhibitor + 2 NRTIs
- Simple?
  - 1 pill daily
- Drug Interactions?
  - Relatively few
  - Polyvalent cations
  - Rifampin
  - Some anticonvulsants
- Well Tolerated?
  - Relatively well tolerated
  - Headache, GI symptoms
  - Weight gain and metabolic symptoms?

TRIUMEQ®
DOLUTEGRAVIR / ABACAVIR/ LAMIVUDINE

- Integrase inhibitor + 2 NRTIs
- Simple?
  - 1 pill daily
- Drug Interactions?
  - Relatively few
  - Polyvalent cations
  - Rifampin
  - Some anticonvulsants
- Well Tolerated?
  - Relatively well tolerated
  - Headache, GI symptoms
  - Abacavir hypersensitivity
  - Weight gain and metabolic symptoms

TIVICAY® + DESCOVY® OR TRUVADA®
DOLUTEGRAVIR + TAF/EMTRICITABINE OR TENOFOVIR DISOPROXYL FUMARATE (TDF)/EMTRICITABINE

- Integrase inhibitor + 2 NRTIs
- Simple?
  - 2 pills daily
- Drug Interactions?
  - Relatively few
  - Polyvalent cations
  - Rifampin
  - Some anticonvulsants
- Well Tolerated?
  - Relatively well tolerated
  - Headache, GI symptoms
  - TDF side effects
  - Weight gain and metabolic symptoms

ISENTRESS® + DESCOVY® OR TRUVADA®
RALTEGRAVIR + TAF/EMTRICITABINE OR TDF/EMTRICITABINE

- Integrase inhibitor + 2 NRTIs

- Simple?
  - 3 pills daily (either all at once or divided into 2 doses)

- Drug Interactions?
  - Relatively few
  - Polyvalent cations
  - Rifampin
  - Some anticonvulsants

- Well Tolerated?
  - Relatively well tolerated
  - Headache, GI symptoms
  - TDF side effects
  - Weight gain and metabolic symptoms?

RECOMMENDED INITIAL REGIMENS: CERTAIN SCENARIOS
INTEGRASE INHIBITOR-BASED REGIMENS

AETC AIDS Education & Training Center Program

Brand Name	Generic Name	Classes Represented	Pill Burden
Genvoya®	Elvitegravir/cobicistat TAF Emtricitabine	INSTI NRTI NRTI	1 pill Once a day
Stribild®	Elvitegravir/cobicistat TDF Emtricitabine	INSTI NRTI NRTI	1 pill Once a day
Isentress® PLUS Epzicom®***	Raltegravir PLUS Abacavir/lamivudine	INSTI PLUS NRTI/NRTI	1 pill twice a day or 2 once a day PLUS 1 pill once a day

*** = HIV RNA must be <100,000

RECOMMENDED INITIAL REGIMENS: CERTAIN SCENARIOS
PROTEASE INHIBITOR-BASED REGIMENS

Brand Name	Generic Name	Classes Represented	Pill Burden
Symtuza®	Darunavir/cobicistat + TAF/emtricitabine	Protease Inhibitor NRTI/NRTI	1 pill Once a day
Prezcobix® or Prezista/Norvir + Epzicom®	Darunavir/cobicistat Or Darunavir/ritonavir + Abacavir/lamivudine	Protease Inhibitor NRTI/NRTI	2-3 pills Once a day
Evotaz® OR Reyataz®/Norvir + Descovy®	Atazanavir/cobicistat OR Atazanavir/ritonavir + TAF/emtricitabine	Protease Inhibitor NRTI/NRTI	2-3 pills Once a day

RECOMMENDED INITIAL REGIMENS: CERTAIN SCENARIOS
NNRTI/NRTI-BASED REGIMENS

Brand Name	Generic Name	Classes Represented	Pill Burden
Delstrigo®	Doravirine TDF* Lamivudine	NNRTI NRTI NRTI	1 pill Once a day
Pifeltro® + Descovy®	Doravirine + TAF/emtricitabine	NNRTI + NRTI x 2	2 pills Once a day
Atripla®	Efavirenz TDF Emtricitabine	NNRTI NRTI NRTI	1 pill Once a day
Symfi®	Efavirenz TDF Lamivudine	NNRTI NRTI NRTI	1 pill Once a day
Sustiva® PLUS Descovy®	Efavirenz TAF/emtricitabine	NNRTI NRTI x 2	2 pills Once a day

RECOMMENDED INITIAL REGIMENS: CERTAIN SCENARIOS
NNRTI/NRTI-BASED REGIMENS

Brand Name	Generic Name	Classes Represented	Pill Burden
Odefsey®***	Rilpivirine TAF Emtricitabine	NNRTI NRTI NRTI	1 pill Once a day
Complera®***	Rilpivirine TDF Emtricitabine	NNRTI NRTI NRTI	1 pill Once a day

*** = HIV RNA must be <100,000 AND CD4 count >200

RECOMMENDED INITIAL REGIMENS IN CERTAIN CLINICAL SITUATIONS

- Other Regimens when NRTIs cannot be used:
  - Darunavir/ritonavir + Lamivudine
  - Darunavir/ritonavir + Raltegravir Twice Daily
    - HIV RNA must be <100,000 and CD4 count >200
  - Dolutegravir + Lamivudine (Dovato®)
  - Dolutegravir + Riplivirine (Juluca®)

FACTORS TO CONSIDER

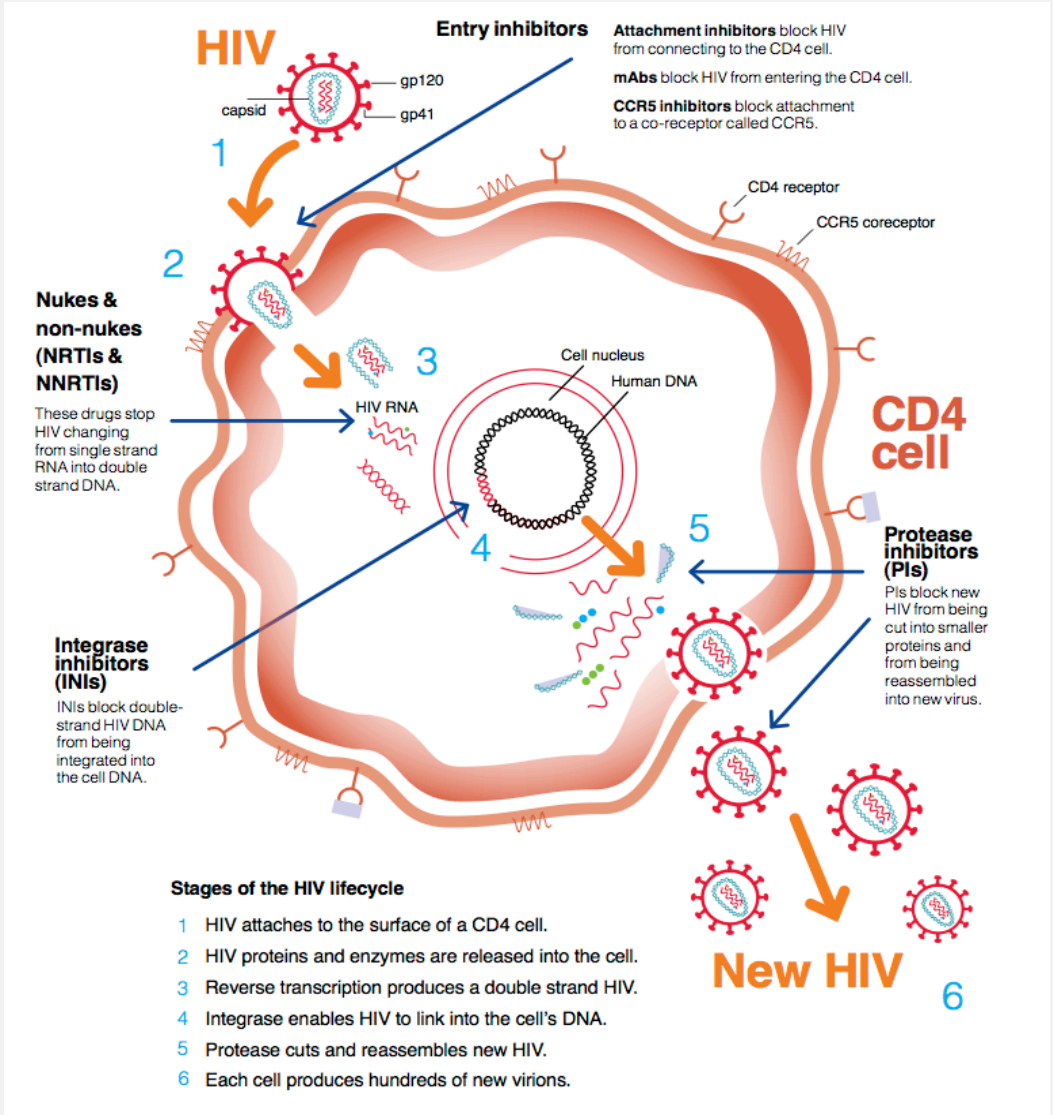
- Comorbidities
  - Cardiovascular disease, hyperlipidemia, renal disease, osteoporosis, psychiatric illness, neurologic disease, drug abuse
- Pregnancy or pregnancy potential
- Coinfections
  - Hepatitis C, Hepatitis B, tuberculosis
- Regimen-Specific Considerations
  - Barrier to resistance
  - Adverse effects
  - Drug interactions
  - Convenience
  - Cost

HIV TREATMENT: TREATMENT EXPERIENCED

- Base ART choice on resistance history
- Three ACTIVE medications when possible
- Do not change just one medication of a failing regimen
- Do not add just one medication to a failing regimen

HIV RESISTANCE

HIV LIFE CYCLE



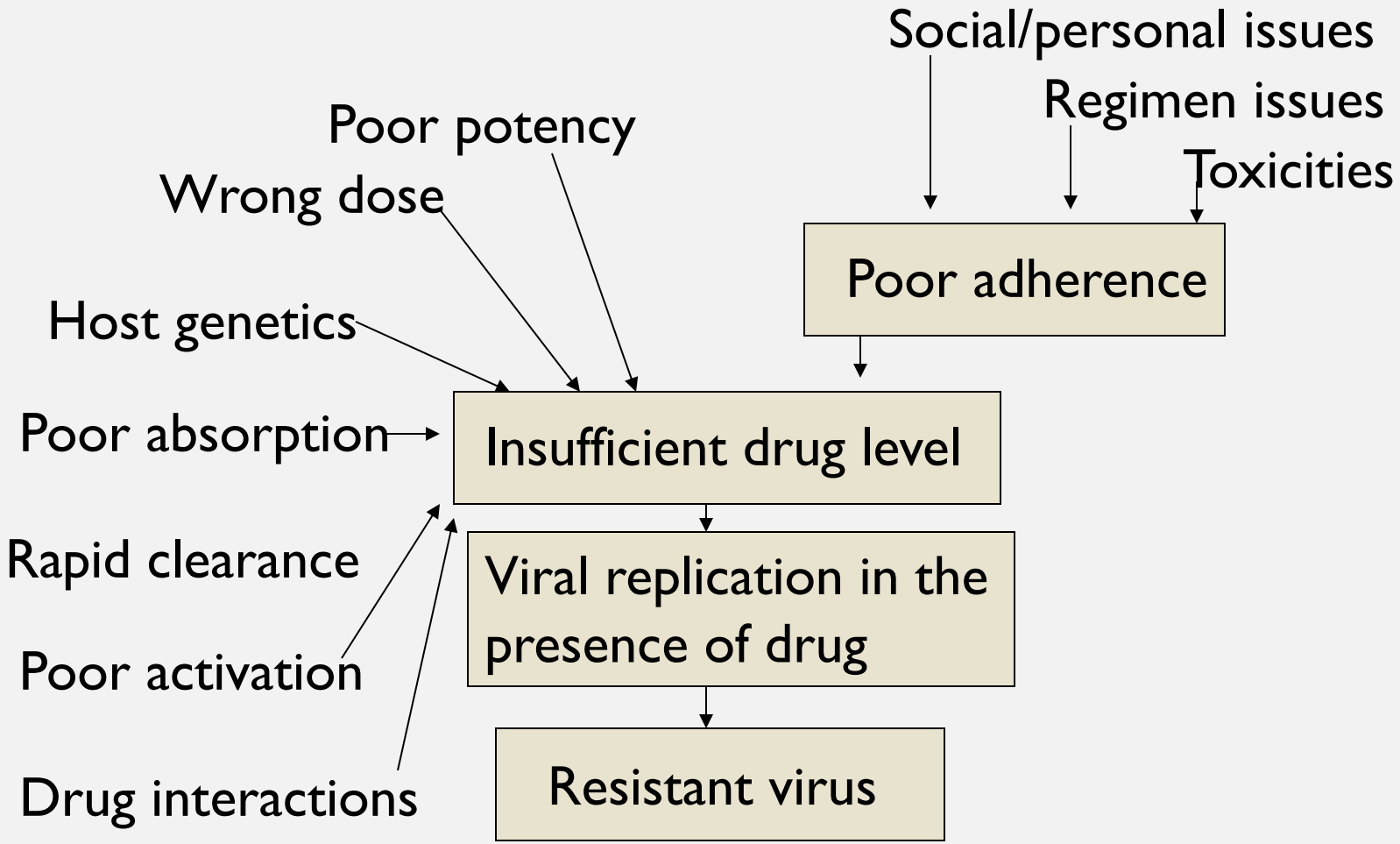
WHAT IS HIV RESISTANCE?

- Ability of HIV to mutate and replicate in the presence of antiretrovirals
- Results in treatment failure and possible further transmission of resistance virus
- Resistance is not a "blanket" term but cross resistance is possible
- Can be acquired or transmitted

HOW DOES HIV RESISTANCE DEVELOP?

- HIV reverse transcriptase is a low-fidelity enzyme
- Mistakes (mutations) lead to mutant strains of HIV
  - Most are inconsequential or result in incompetent strains of HIV
  - A small number confer resistance to currently available antiretroviral drugs
- Insufficiently potent antiretrovirals exerts reproductive pressure that selects for resistance-bearing strains

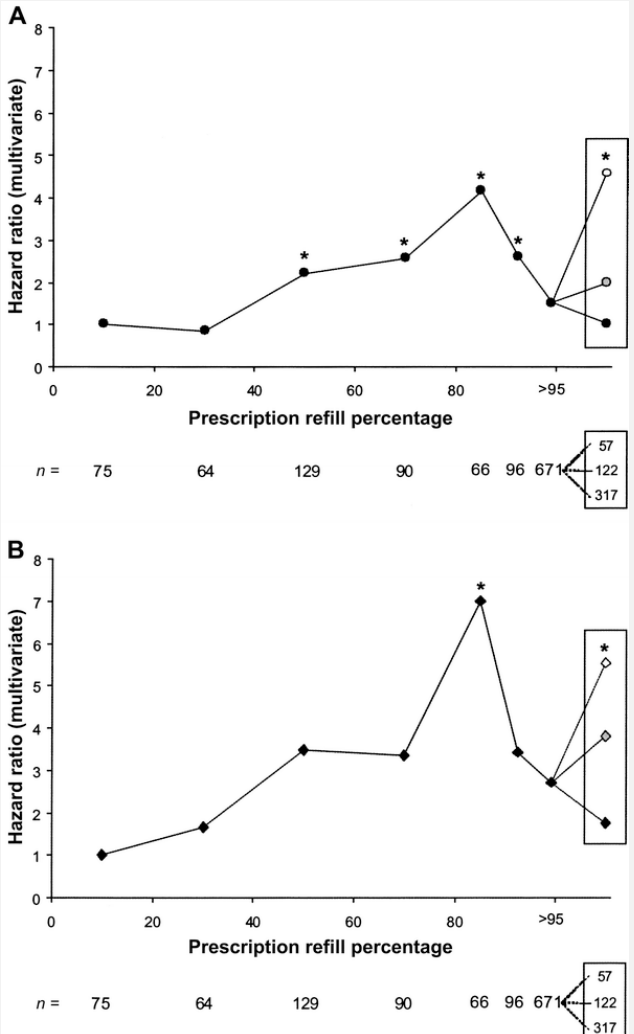
HOW ARE ANTIRETROVIRALS "INSUFFICIENTLY POTENT"?



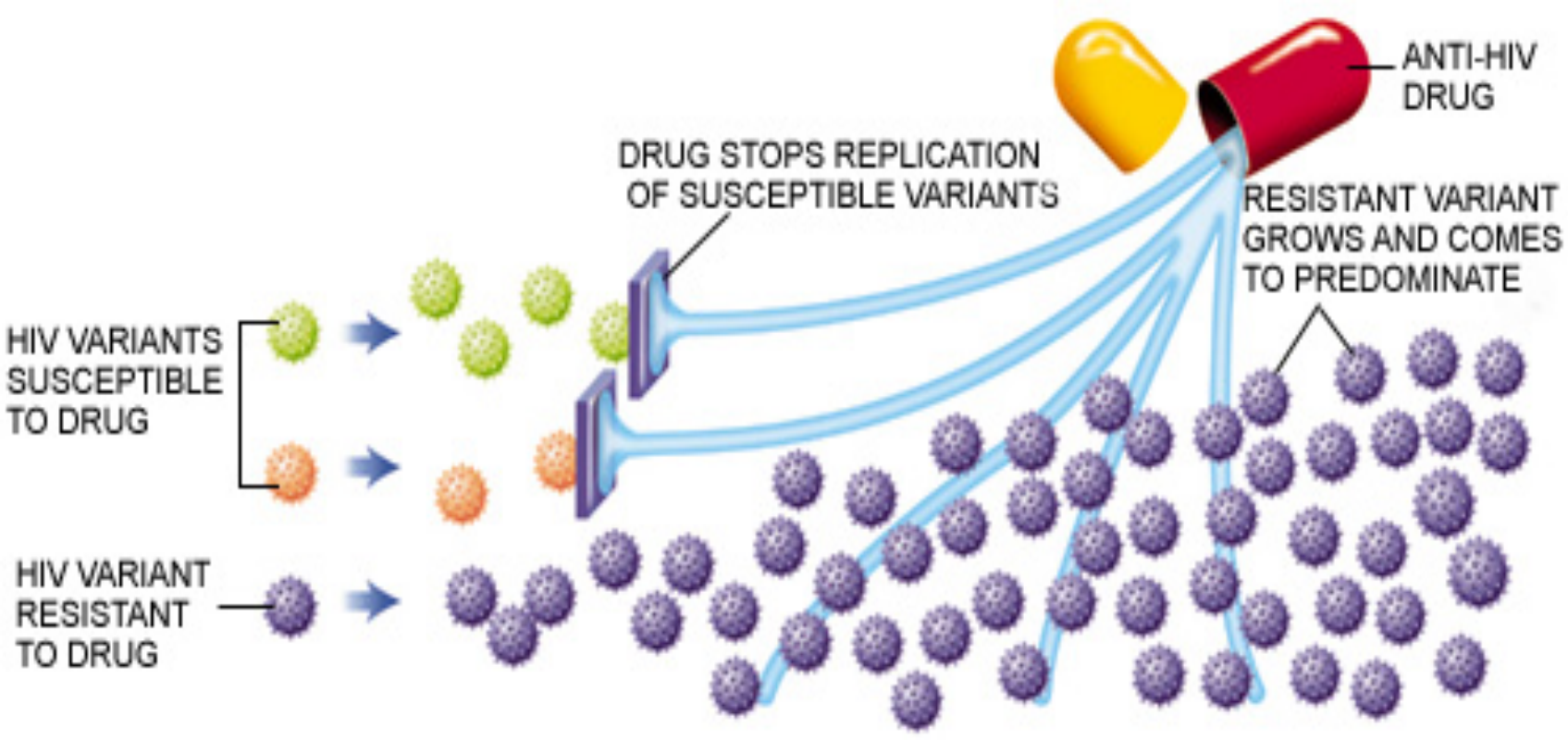
What is the relationship between adherence and resistance?

Harrigan, JID, 2005

- Prospective, observational study
- N = 1191
- Predictors of resistance
  - High baseline VL
  - Good (not great) adherence

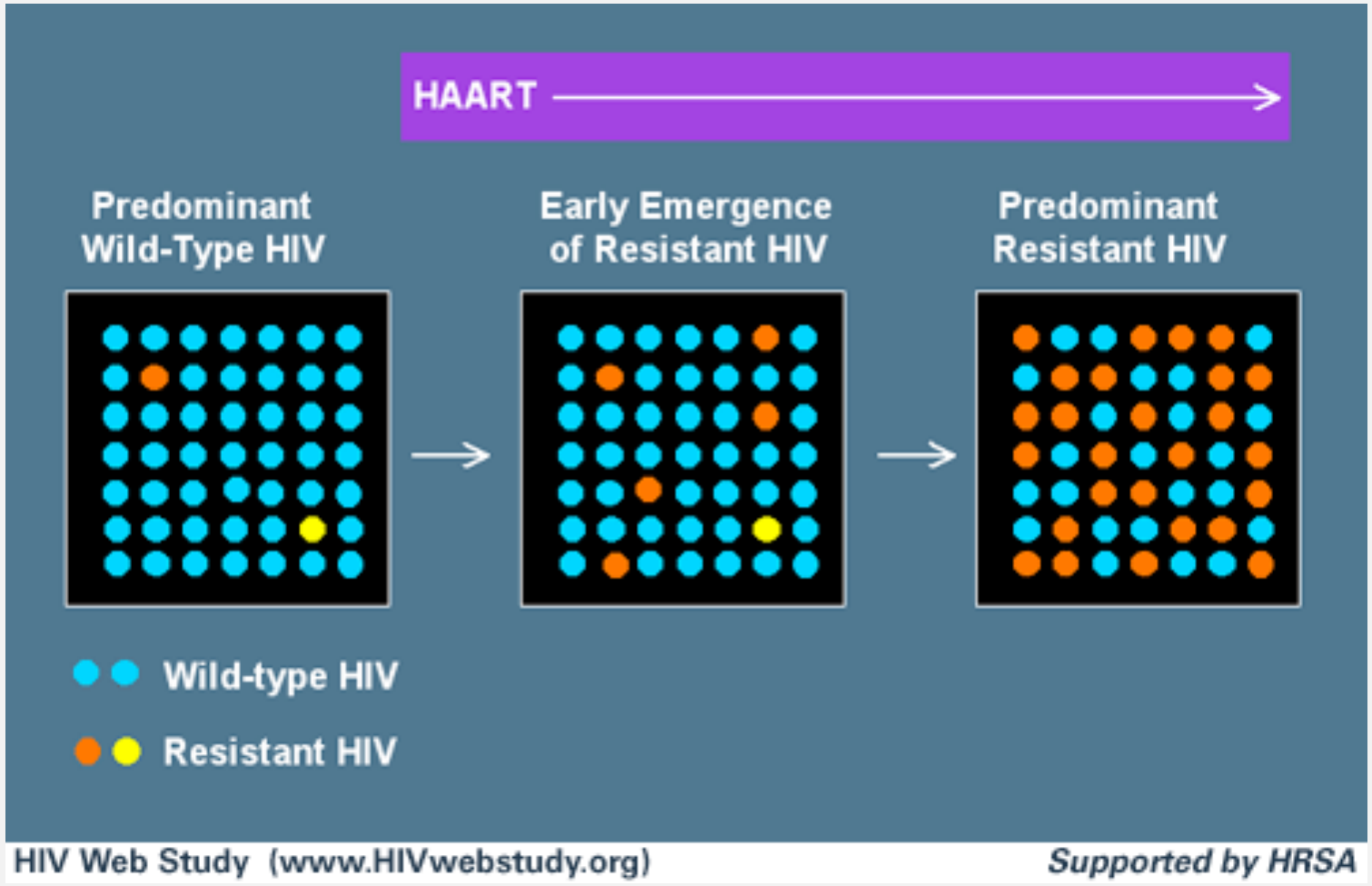


HOW ARE RESISTANT STRAINS SELECTED?



How drug resistance arises. Richman, DD. Scientific American , July 1998

HOW ARE RESISTANT STRAINS SELECTED?



HIV RESISTANCE TRANSMISSION

- 6.6-11% of new transmission will have transmitted resistance
- Most common is NRTIS and NNRTIs
- Less common for PIs
- Rare for INSTIs
- Associated with:
  - Prevalence of mutation
  - Fitness cost of mutation

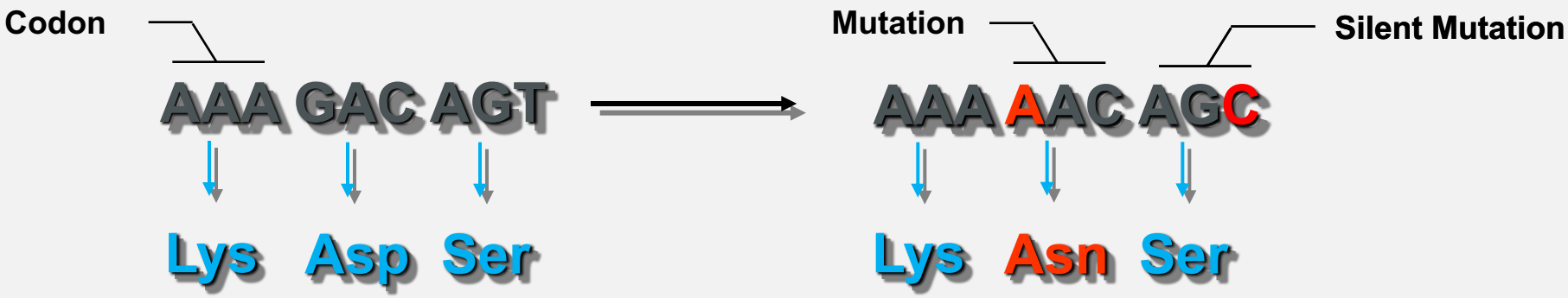
HOW DO WE TEST FOR RESISTANCE?

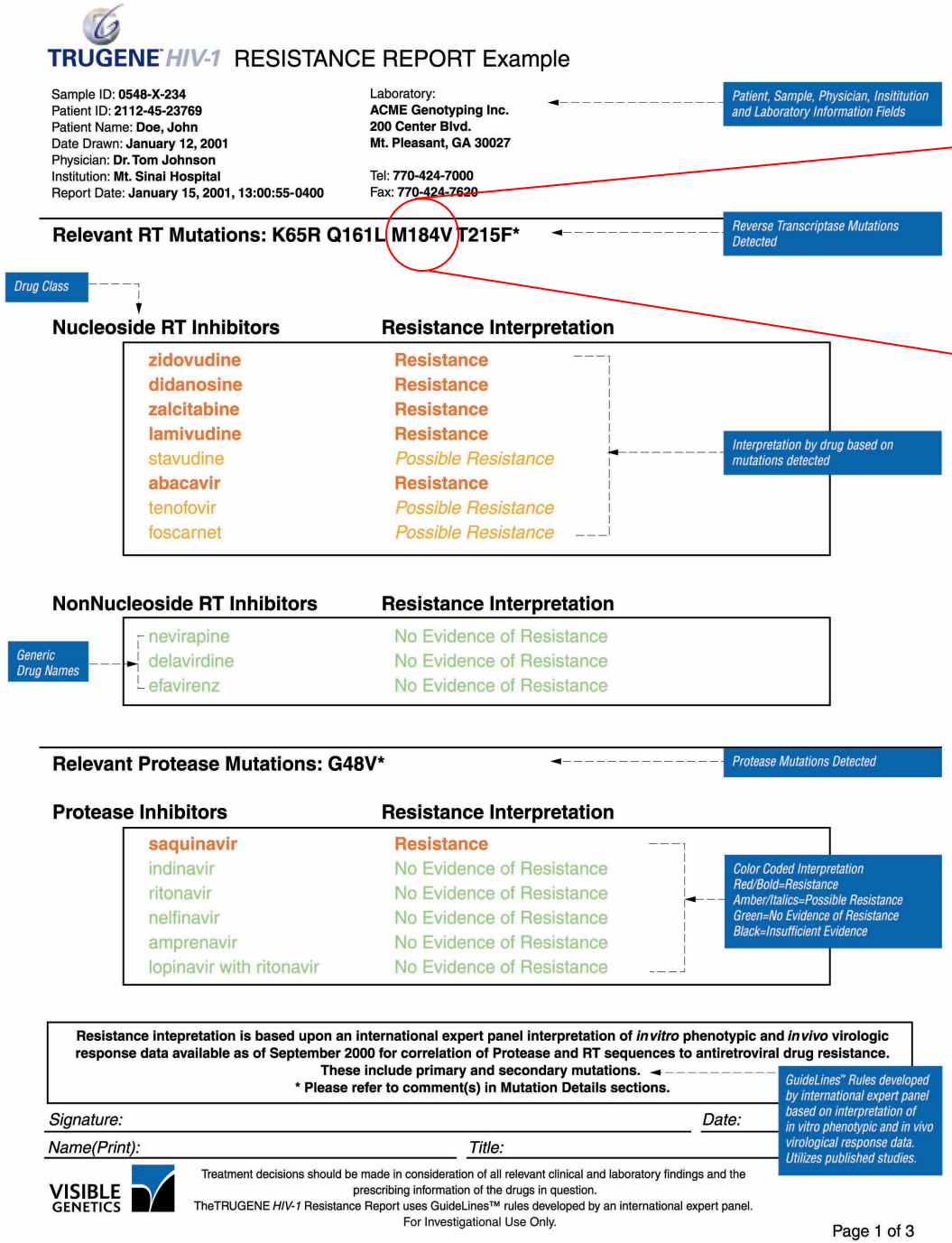
1. Genotype
2. Phenotype
3. Archived Genotype

GENOTYPIC RESISTANCE ASSAY

- Sequences relevant portions of the HIV genome coding for Reverse Transcriptase, Protease enzymes, and Integrase enzymes

- Detects and reports variations in the sequences of these genes that are known or suspected to confer antiretroviral resistance





M = Methionine
184 = the codon #
V = Valine

A mutation at codon #184 in the gene Reverse Transcriptase codes for a Valine residue where normally a Methionine residue is found.

MAJOR NRTI MUTATIONS

Consensus	184 M	65 K	70 K	74 L	115 Y	41 M	67 D	70 K	210 L	215 T	219 K	69 T	151 Q
3TC	VI	R										Ins	M
FTC	VI	R										Ins	M
ABC	VI	R	E	VI	F	L			W	FY		Ins	M
DDI	VI	R	E	VI		L			W	FY		Ins	M
TDF	***	R	E		F	L		R	W	FY		Ins	M
D4T	***	R	E			L	N	R	W	FY	QE	Ins	M
ZDV	***	***	*	*		L	N	R	W	FY	QE		

Stanford Database https://hivdb.stanford.edu/

MAJOR NNRTI MUTATIONS

Consensus	100 L	101 K	103 K	106 V	138 E	181 Y	188 Y	190 G	230 M
DOR	I	EP		AMI		CIV	LHC	SE	L
EFV	I	EP	NS	AM		CIV	LCH	ASE	L
ETR	I	EP			AGKQ	CIV	L	ASE	L
NVP	I	EP	NS	AM		CIV	LCH	ASE	L
RPV	I	EP			AGKQ	CIV	L	ASE	L

Stanford Database https://hivdb.stanford.edu/

MAJOR PI MUTATIONS

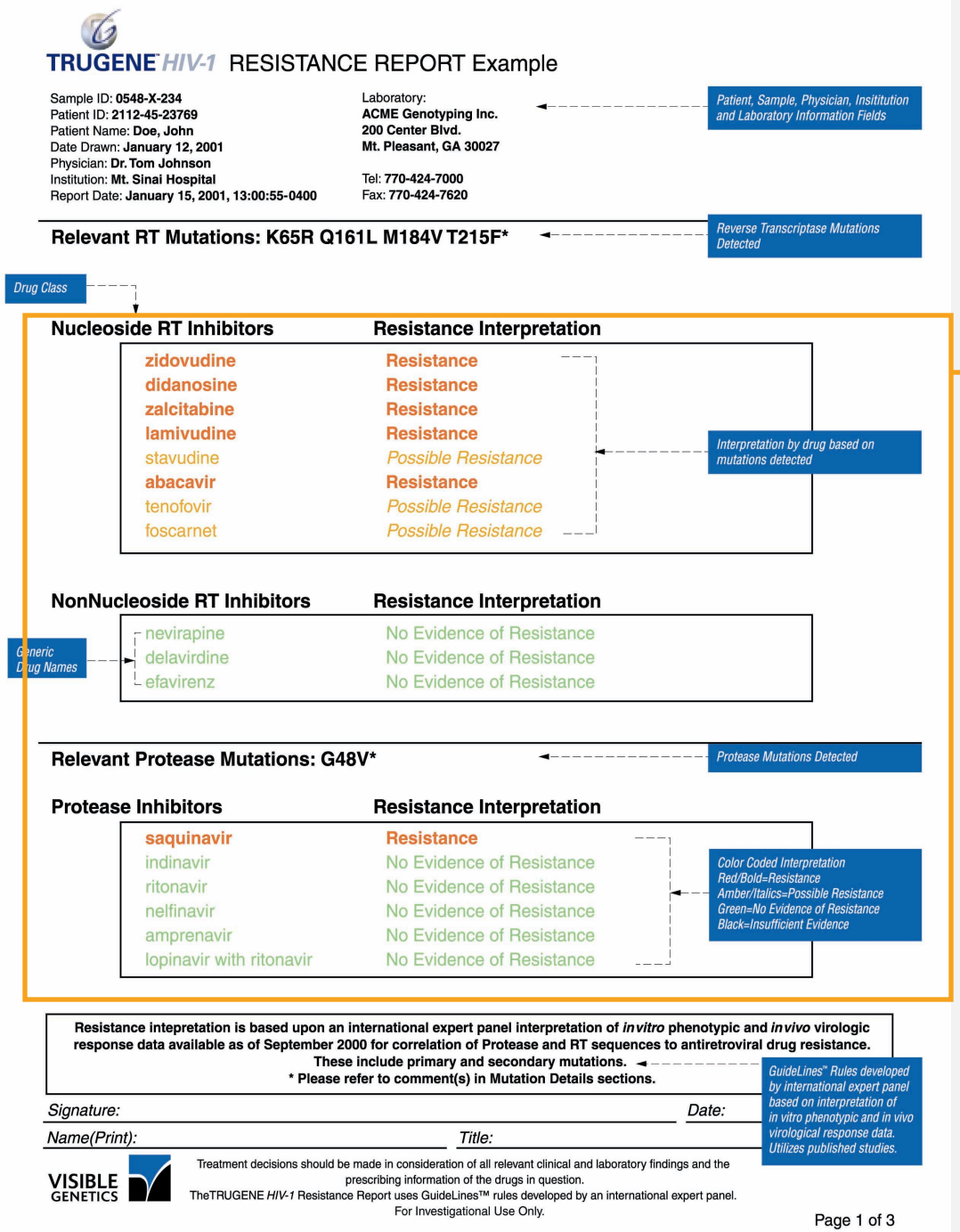
Consensus	30 D	32 V	33 L	46 M	47 I	48 G	50 I	54 I	76 L	82 V	84 I	88 N	90 L
ATV/r		I	F	IL	V	**VM**	**L**	VTALM		ATFS	**V**	**S**	**M**
DRV/r		**I**	F		**VA**		**V**	**LM**	**V**	F	V		
FPV/r		**I**	**F**	**IL**	**VA**		**V**	VTA**LM**	**V**	ATS**F**	**V**		**M**
IDV/r		**I**		**IL**	V			**VTA**LM	**V**	**AFTS**	**V**	S	**M**
LPV/r		**I**	F	IL	V**A**	VM	**V**	**VTALM**	**V**	**AFTS**	**V**		M
NFV	**N**		F	**IL**	V	**VM**		**VTALM**		**AFTS**	**V**	**DS**	**M**
SQV/r						**VM**		**VTA**LM		AT	**V**	S	**M**
TPV/r		I	F	IL	**VA**			**VAM**		**TL**	**V**		

Stanford Database https://hivdb.stanford.edu/

MAJOR INSTI MUTATIONS

Consensus	66 T	92 E	118 G	138 E	140 G	143 Y	147 S	148 Q	155 N	263 R
Bictegravir (BIC)	K	Q	R	KAT	SAC			**HRK**	H	K
Dolutegravir (DTG)	K	Q	R	KAT	SAC			**HRK**	H	K
Elvitegravir (EVG)	**AIK**	**Q**	**R**	**KAT**	**SAC**		**G**	**HRK**	**H**	**K**
Raltegravir (RAL)	AI**K**	**Q**	**R**	**KAT**	**SAC**	**RCH**		**HRK**	**H**	K

Stanford Database https://hivdb.stanford.edu/



Interpretation of the results: what are the clinical implications of these mutations in terms of resistance to antiretroviral agents?

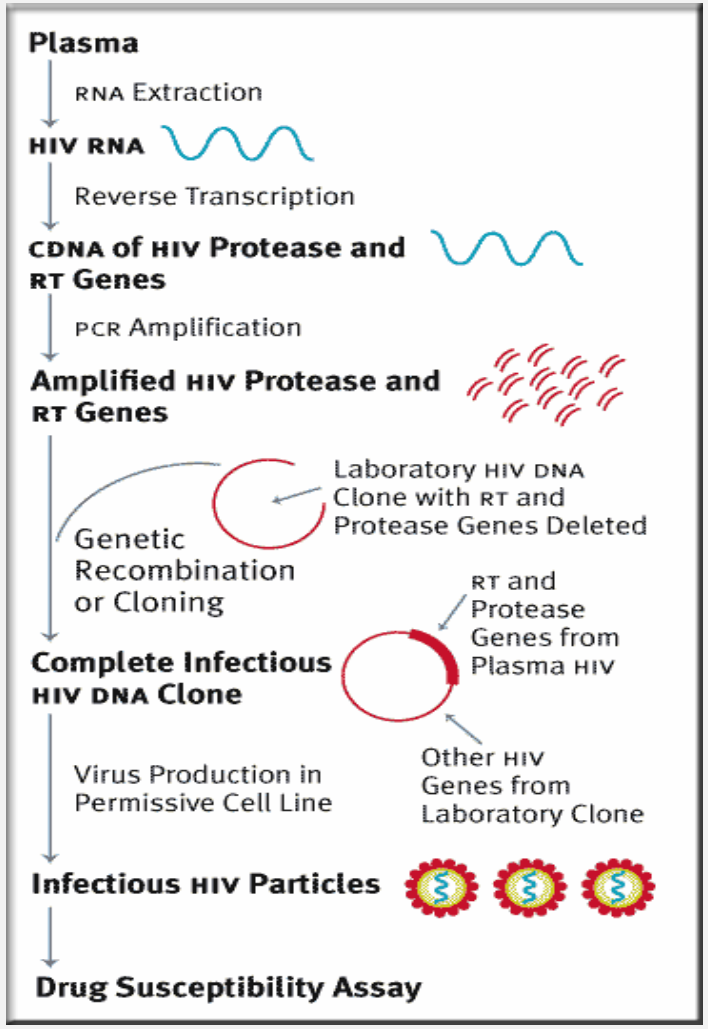
INTERPRETATION OF THE GENOTYPIC RESISTANCE ASSAY

- Genotype report includes an interpretation of the clinical implications of the identified mutations

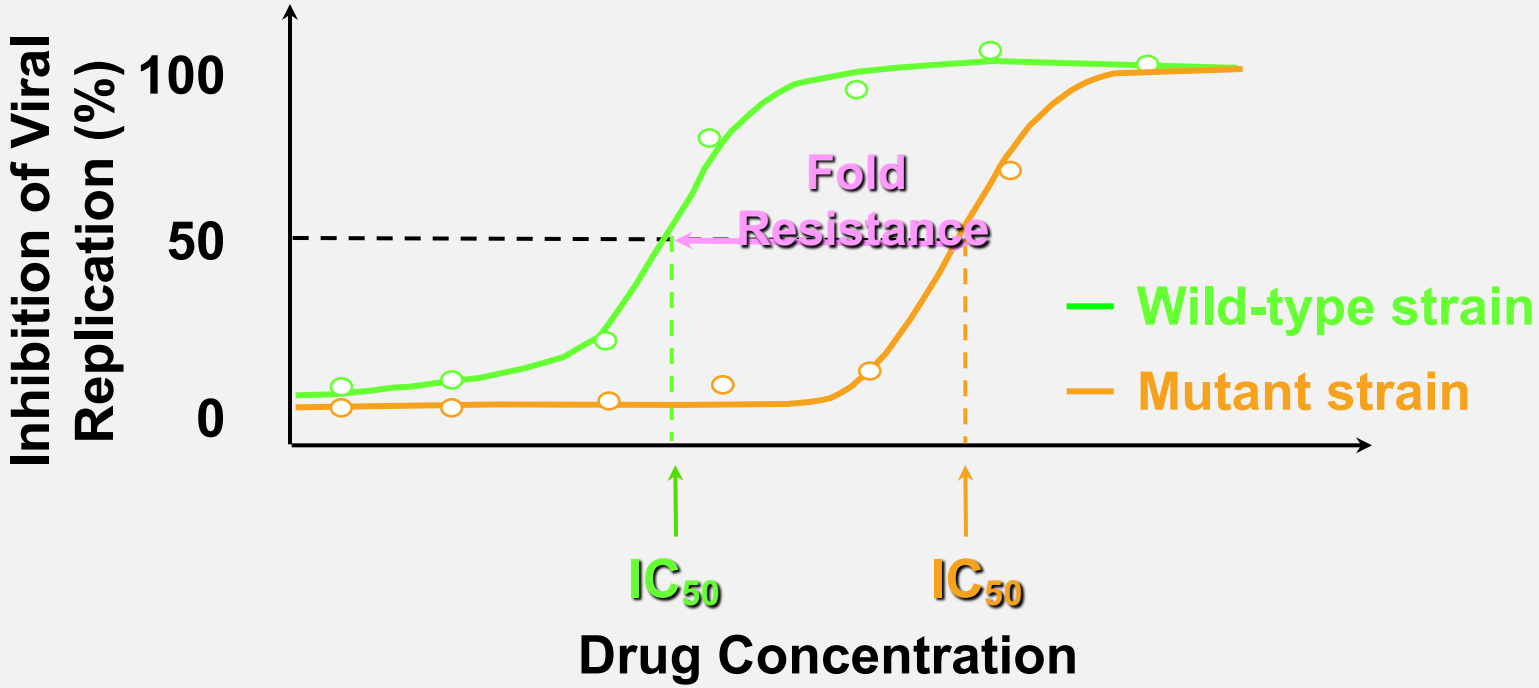
- Issues:
  - The exact significance of some mutations are either debatable or inconsistent
  - Interactions between mutations complicate estimation of the clinical impact
  - Interpretation of genotypic resistance assays is not standardized across different laboratories
  - Assays will not detect minority resistant strains (less than 10-20% of the viral population)
  - Reversion to wild-type virus while off antiretrovirals

PHENOTYPIC RESISTANCE TESTING

- Tests viability of a synthetic version of the patient's HIV in the presence of antiretroviral agents
- Akin to bacterial antibiotic susceptibility assays
- Results reported as fold-change in susceptibility to antiretroviral agents

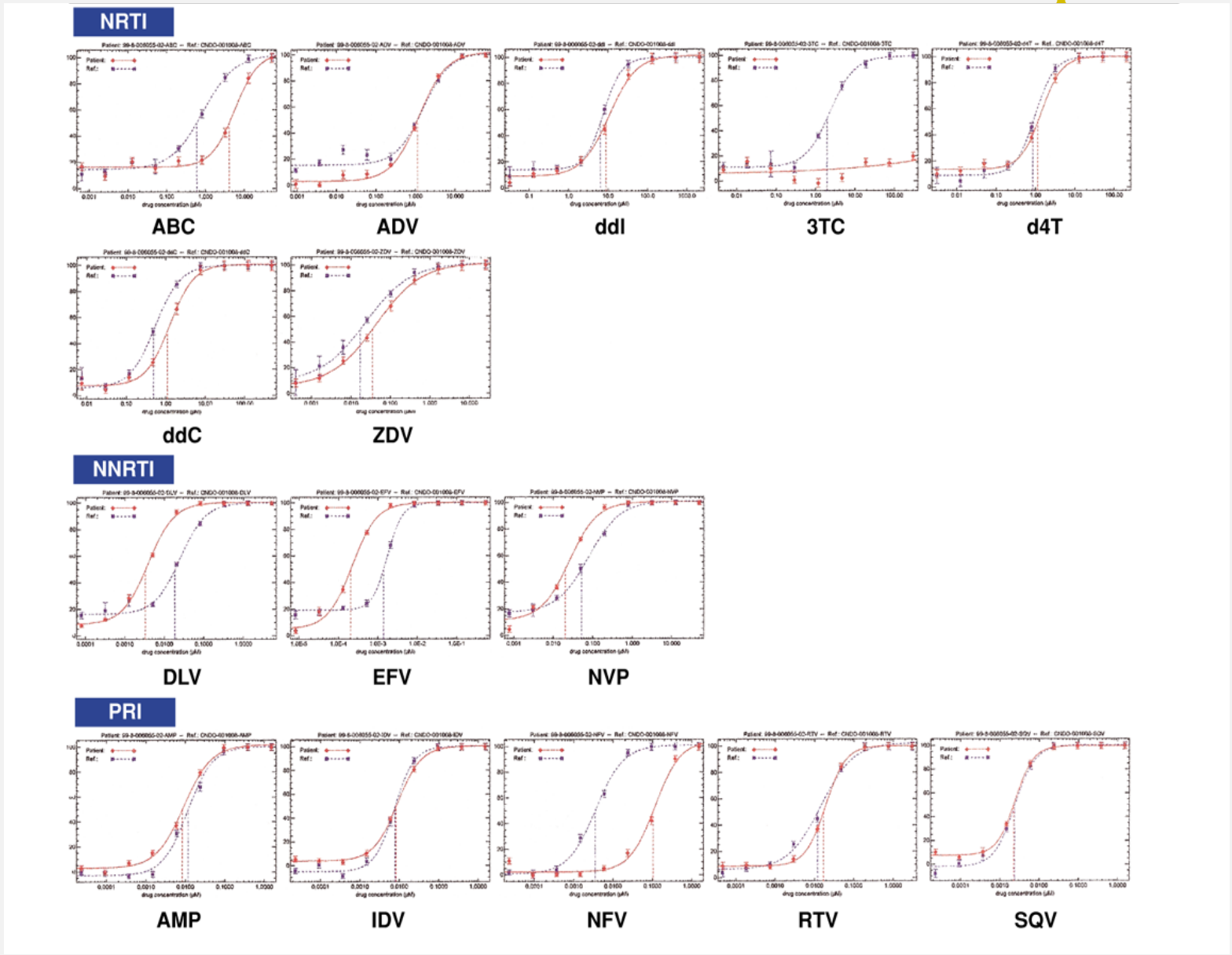


PHENOTYPE RESISTANCE TESTING

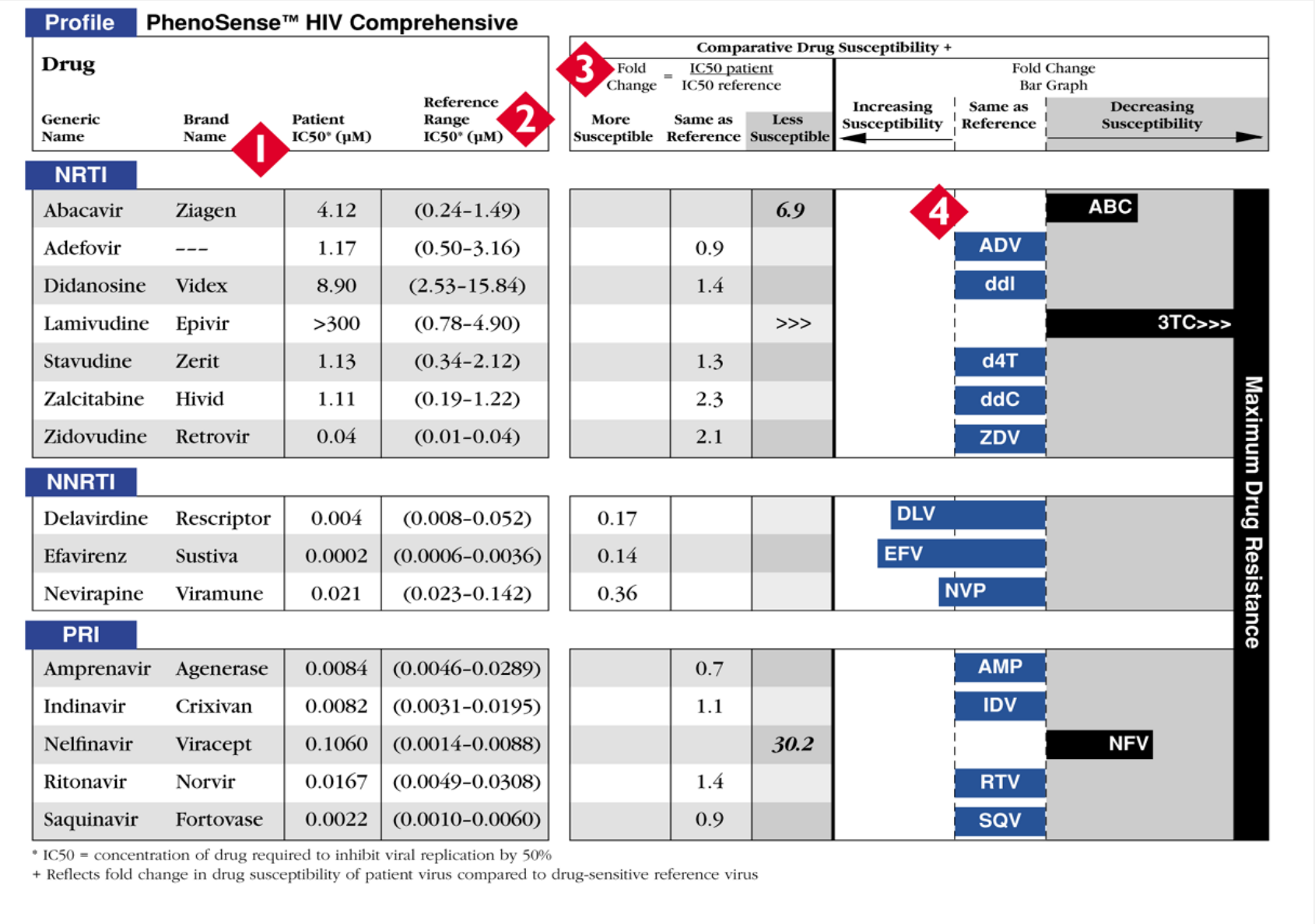


Reviewed in Wilson. *AIDS Read* 2000;10:469.

PhenoSense HIV Patient Report



PhenoSense™ HIV Report



Profile PhenoSense™ HIV Comprehensive

Drug: Generic Name	Brand Name	Patient IC50* (µM)	Reference Range IC50* (µM)	Comparative Drug Susceptibility + (Fold Change = IC50 patient / IC50 reference): More Susceptible	Same as Reference	Less Susceptible
NRTI						
Abacavir	Ziagen	4.12	(0.24–1.49)			*6.9*
Adefovir	---	1.17	(0.50–3.16)		0.9	
Didanosine	Videx	8.90	(2.53–15.84)		1.4	
Lamivudine	Epivir	>300	(0.78–4.90)			>>>
Stavudine	Zerit	1.13	(0.34–2.12)		1.3	
Zalcitabine	Hivid	1.11	(0.19–1.22)		2.3	
Zidovudine	Retrovir	0.04	(0.01–0.04)		2.1	
NNRTI						
Delavirdine	Rescriptor	0.004	(0.008–0.052)	0.17		
Efavirenz	Sustiva	0.0002	(0.0006–0.0036)	0.14		
Nevirapine	Viramune	0.021	(0.023–0.142)	0.36		
PRI						
Amprenavir	Agenerase	0.0084	(0.0046–0.0289)		0.7	
Indinavir	Crixivan	0.0082	(0.0031–0.0195)		1.1	
Nelfinavir	Viracept	0.1060	(0.0014–0.0088)			*30.2*
Ritonavir	Norvir	0.0167	(0.0049–0.0308)		1.4	
Saquinavir	Fortovase	0.0022	(0.0010–0.0060)		0.9	

Fold Change Bar Graph: Increasing Susceptibility ◄ | Same as Reference | Decreasing Susceptibility ►

ABC, ADV, ddI, 3TC>>>, d4T, ddC, ZDV, DLV, EFV, NVP, AMP, IDV, NFV, RTV, SQV

Maximum Drug Resistance

* IC50 = concentration of drug required to inhibit viral replication by 50%

+ Reflects fold change in drug susceptibility of patient virus compared to drug-sensitive reference virus

WHICH RESISTANCE ASSAY IS BETTER?

	Pros	Cons
Genotypic assay	• More clinical experience and evidence of clinical utility • Less expensive •Results available in 1-2 weeks	• May not account for some variability in interpretation •May miss mutations present in less common strains •Requires at least 500 copies of HIV RNA per unit of blood
Phenotypic assay	• Simpler to interpret • More directly estimates net effect of multiple mutations	•Less evidence of clinical utility •More expensive •Results in 3-4 weeks •May miss mutations present in less common strains

ARCHIVED GENOTYPE

- Amplifies proviral HIV DNA from infected cells
- No restrictions on minimum circulating HIV RNA
- In theory, provides mutation history including but not limited to the HIV species predominantly circulating
- Utility is still up for debate

COMMON/SIGNIFICANT MUTATIONS

- NRTI
  - M184V
  - K65R
  - M41L, L210W, T215F/Y
  - 69 Insertion
- NNRTI
  - K103N
  - L100I
  - Y188L
- Protease Inhibitors
  - I50L/V
  - I54L/M
  - L90M
- INSTI
  - E92Q
  - Q148H/R/K

TREATMENT IMPLICATIONS OF RESISTANCE

- Typically makes HIV more difficult to treat
  - More pills
  - More frequent administrations
  - Increased interactions, side effects
  - Increased expense
- Full resistance history must be considered
- Following treatment principles usually remains both desirable and possible
- Consider expert consultation

EXPERT CONSULTATION RESOURCES

- Internet:
  - DHHS Treatment Guidelines
  - http://hivdb.stanford.edu
  - https://www.iasusa.org/resources/hiv-drug-resistance-mutations/

- SE-AETC – email **clare.bolds@vumc.org**

- National Clinicians' Telephone Consultation Service (Warmline): 800-933-3413

CONCLUSION/SUMMARY

- HIV treatment involves using 3 fully active meds representing at least 2 class of ART
- Integrase inhibitors along with a two NRTIs are currently the preferred regimen for treatment naïve
- HIV drug resistance is a significant issue occurring with subtherapeutic levels of antiretrovirals
- Testing HIV resistance is readily done most commonly with a Genotypic Assay
- HIV resistance has significant treatment implications often leading to more complex regimens