TACKLING ART RESISTANCE

MANAGEMENT OF TREATMENT EXPERIENCED HIV PART 1

Linda Robinson BSc.Phm, AAHIVP

HIV Pharmacotherapy Specialist

Past-Chair CHAP: 2013 & 2021

We acknowledge the 46 treaties and other agreements ……

LAND ACKNOWLEDGEMENT

…that cover the territory now called Ontario. We are thankful to be able to work and live in these territories. We are thankful to the First Nations, Metis and Inuit people who have cared for these territories since time immemorial and who continue to contribute to the strength of Ontario and to all communities across the province.

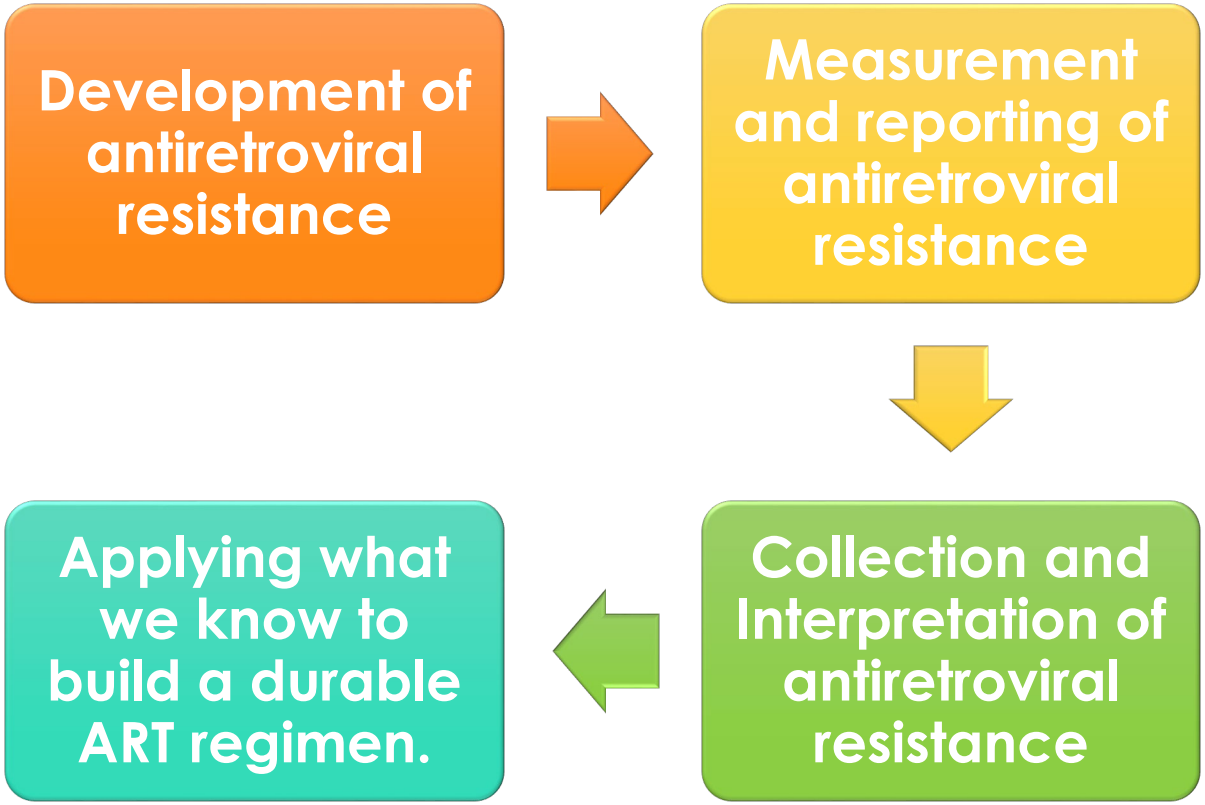
DISCLAIMER/DISCLOSURE

- Speaker Honoraria
  Merck, BMS, ViiV, Gilead, Janssen, Abbvie
- Consulting fees
  Gilead, Janssen, BMS
- Contracted for CME production/presentation
  ViiV, Janssen, BMS, Merck, Gilead, Abbvie

The opinions and format of this education module are those of Linda Robinson, offering hints and strategies learned throughout her career. It was supported by an unrestricted educational grant through CHAP Education Projects.

Special thanks to Merck for the unrestricted grant for this particular inaugural educational series.

LEARNING OBJECTIVES



Sometimes a short walk down memory lane is all it takes to appreciate where you are today.

- Susan Gale

boardofwisdom.com

ART DEVELOPMENT TIMELINE

1995 → 2015 → 2025

ART DEVELOPMENT TIMELINE

1995

2015

2026

HIV THERAPY IN 2002: WHAT WE KNEW

1. Being on treatment will increase your lifespan and decrease the risk of AIDS & non-AIDS conditions.

2. Don't let the immune system become too depleted before starting therapy

HIV THERAPY IN 2024: WHAT WE KNOW

1. Modern treatment will normalize your lifespan and virtually eliminate the risk of AIDS & non-AIDS conditions.

2. The earlier you start, the better, regardless of viral load or immune status

3. Simple, yet durable, is the best option for the ART regimen AND patient longevity.

WHEN TO CHANGE THERAPY

- When it is no longer working
- When the patient wants to
- When something better comes along

REASONS FOR REGIMEN SIMPLIFICATION/MODERNIZATION

- Decrease pill burden
- Simplify dosing times
- Reduce Side Effects
- Avoid Drug Interactions
- Cost savings?

GOALS OF HIV TREATMENT

- Maximal and durable suppression of viral load
- Restoration and/or preservation of immunologic function
- Reduction of HIV-related morbidity and mortality
- Improvement of quality of life

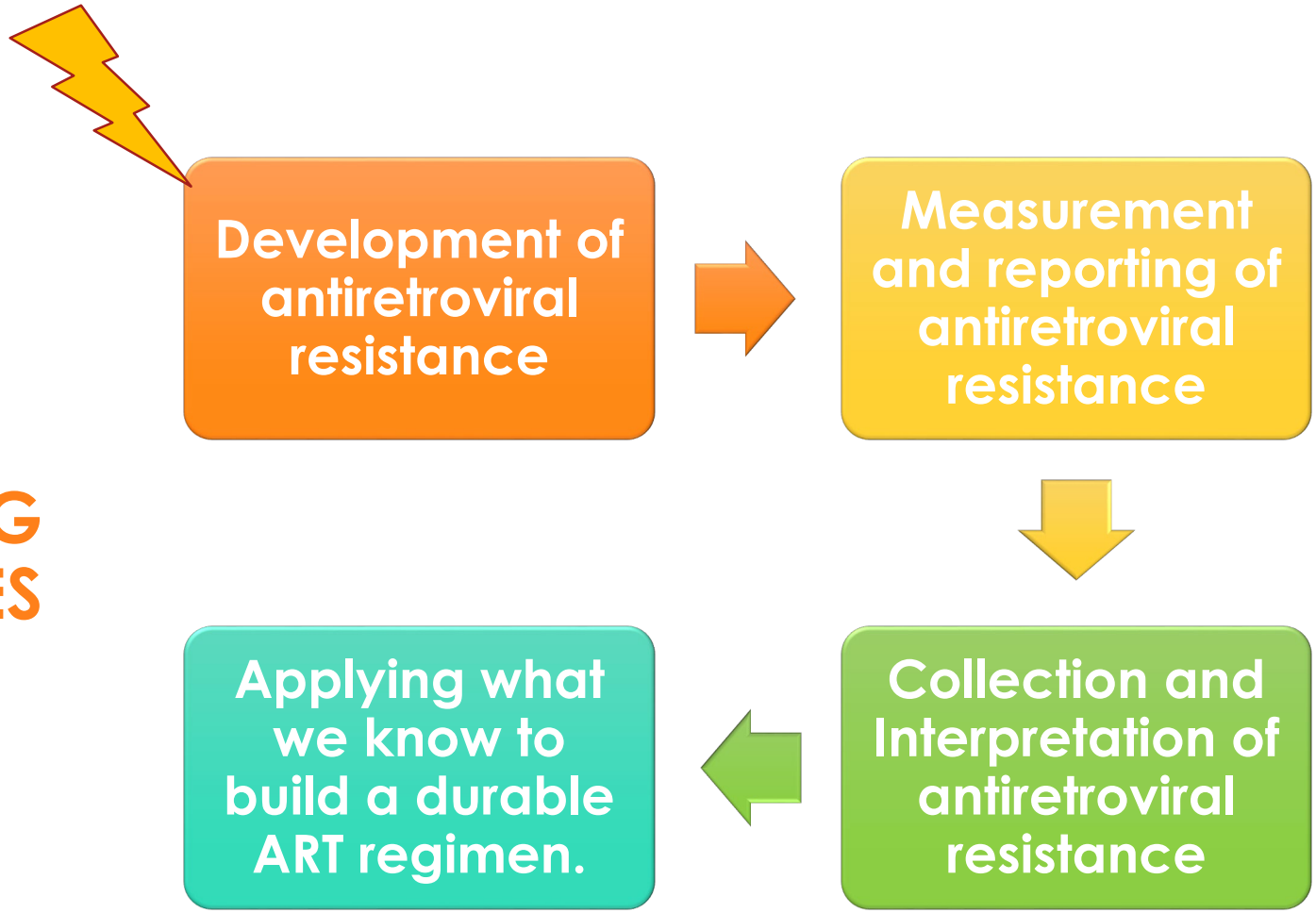
➢ PREVENTION OF TRANSMISSION

➢ ENGAGMENT AND RE-ENGAGEMENT

➢ SAFETY and LONGEVITY

➢ SIMPLIFICATION/MODERNIZATION

LEARNING OBJECTIVES



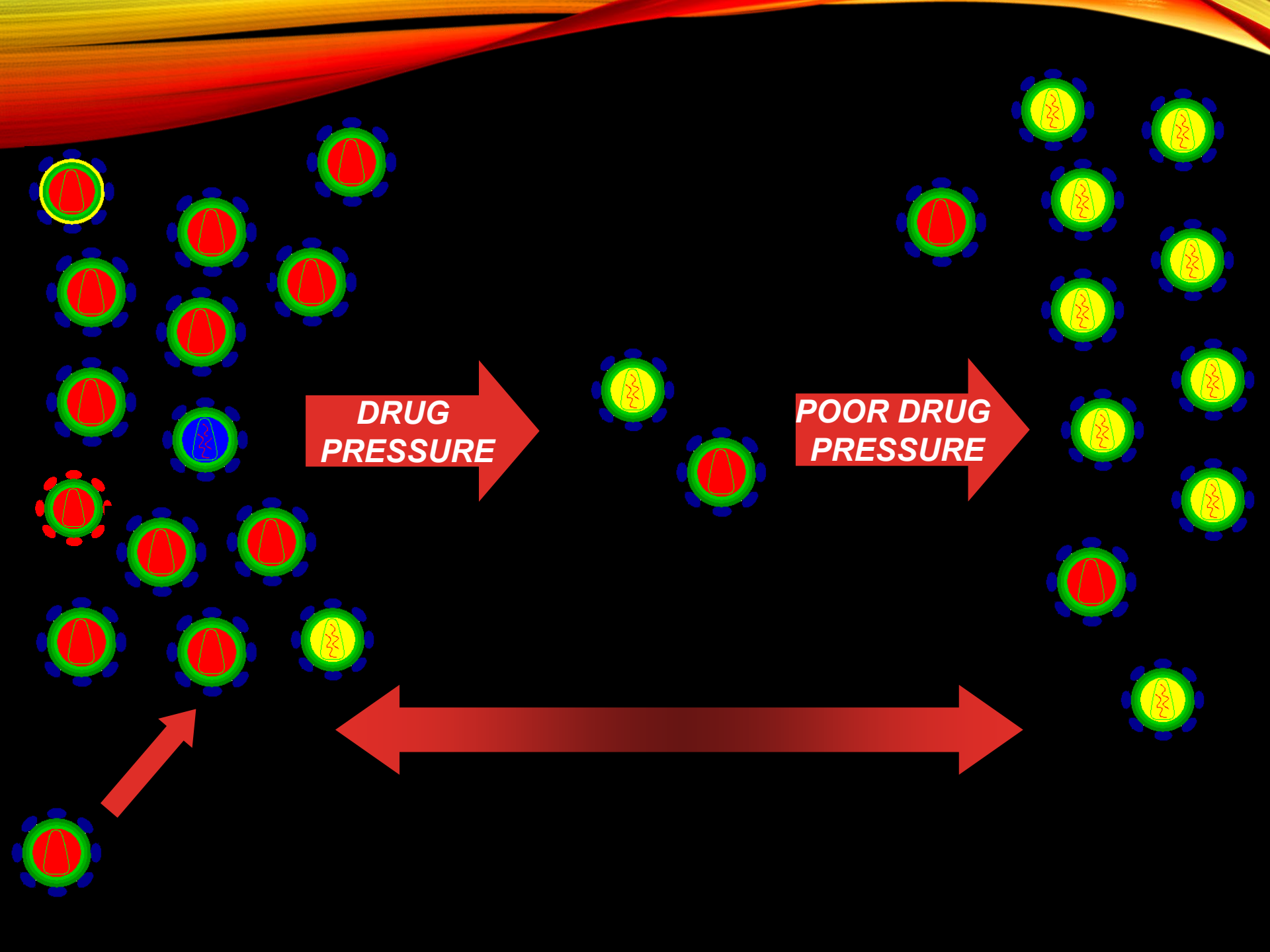
TYPES OF RESISTANCE

PRIMARY (transmitted) RESISTANCE

The virus that is transmitted upon infection is a mutated, antiretroviral resistant 'quasispecies' of HIV.

ACQUIRED RESISTANCE

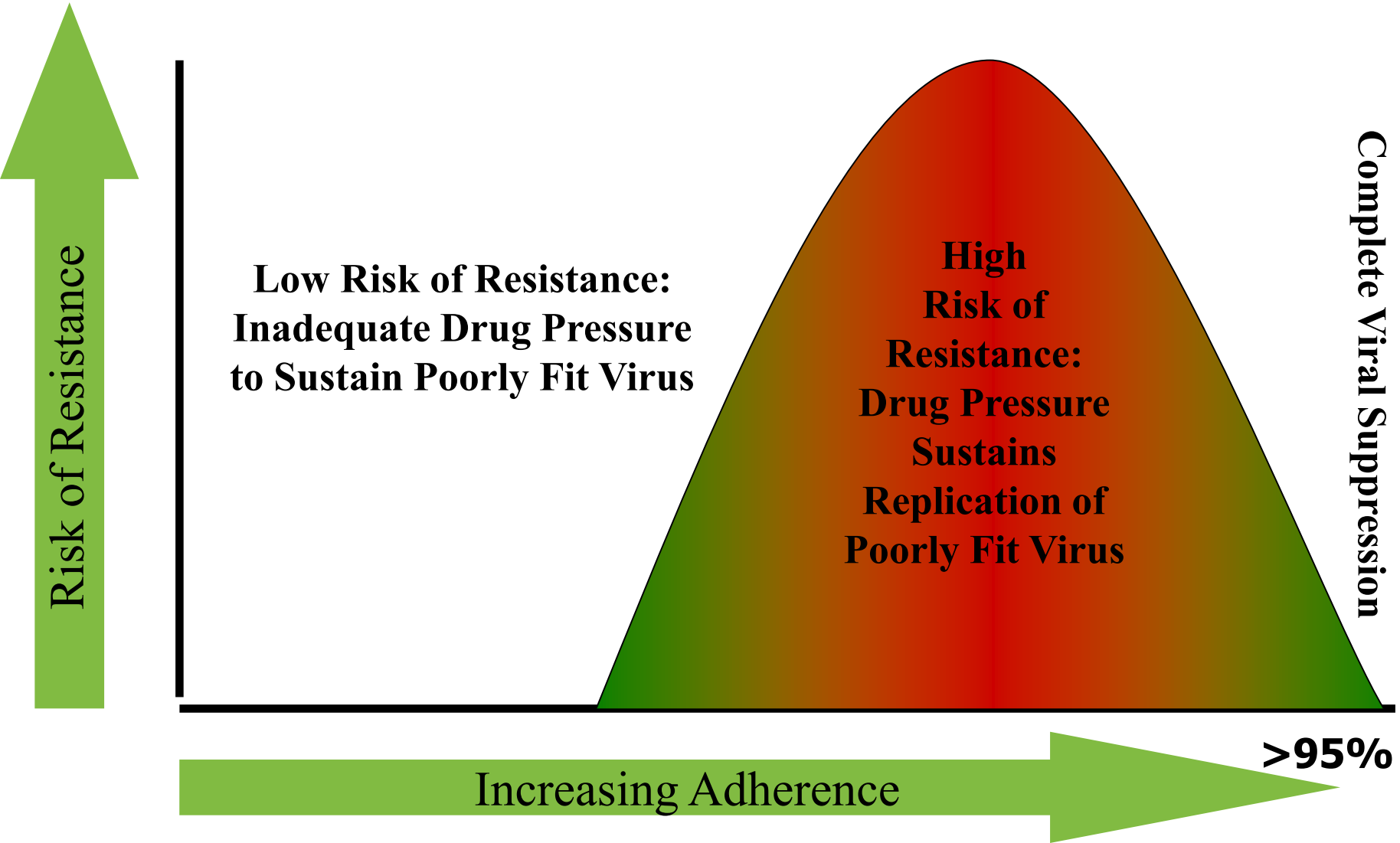
A 'quasispecies' or mutant strain of HIV evolves as the dominant strain under suboptimal antiretroviral pressure.


DRUG PRESSURE
POOR DRUG PRESSURE

"POOR DRUG PRESSURE"

- Pharmacokinetic reasons:
  - Absorption
  - Metabolism
  - Distribution
  - Excretion
- Choice of medications and/or incorrect dosing
- POOR ADHERENCE!
- Genetic Barrier to Resistance

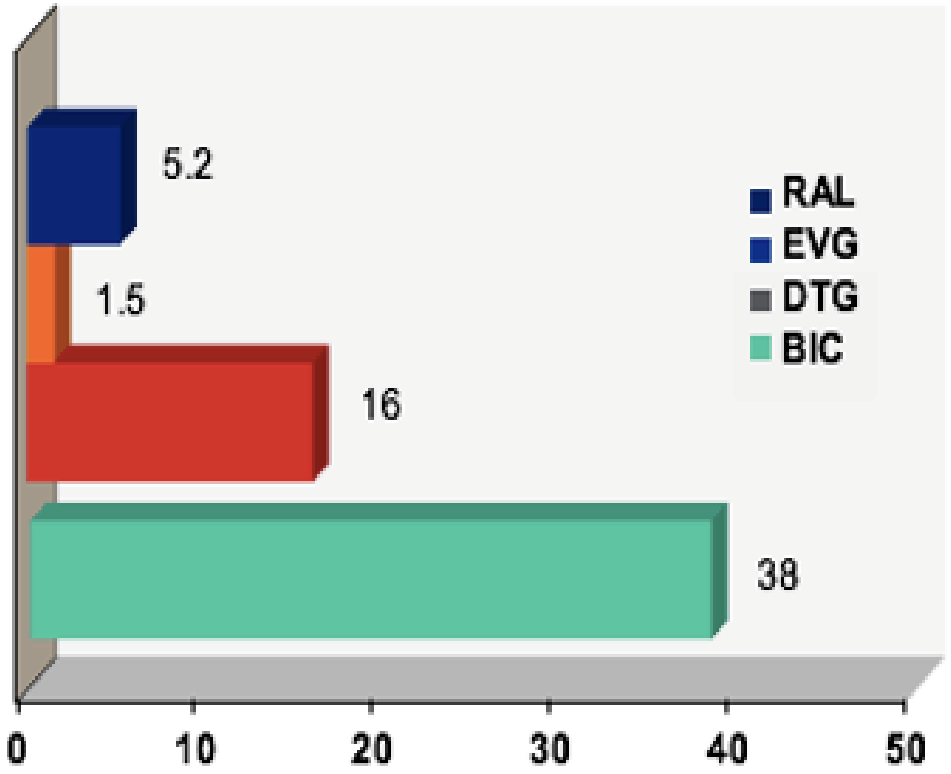
ADHERENCE & RISK OF RESISTANCE



THE FORGIVENESS FACTOR

- 2 drug vs 3 drug
- “missed doses”
- Pharmacokinetic Improvements
- The chemistry of drug design

Dissociation Half-life of INSTIs



Wild Type HIV-1 IN Dissociation $T_{1/2}$

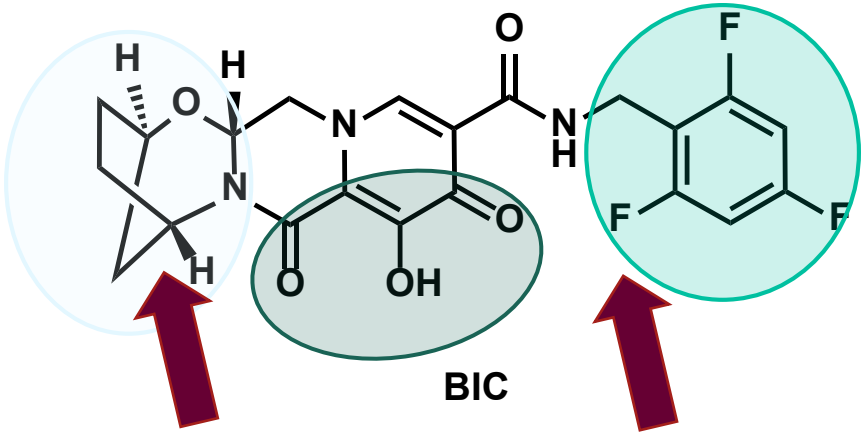
- BIC vs DTG (p=0.017)
- BIC vs RAL (p=0.003)
- BIC vs EVG (p=0.0006)

The dissociation half-life of BIC from wild type HIV-1 integrase-DNA complexes is twice as long as DTG

NOVEL CHEMICAL STRUCTURE: BICTEGRAVIR

Side Chain:

- Bridging ***bic***yclic ring
- Metabolic stability
- Allows favorable low levels of free fraction in plasma
- Low PXR activation leading to no CYP3A induction[3]



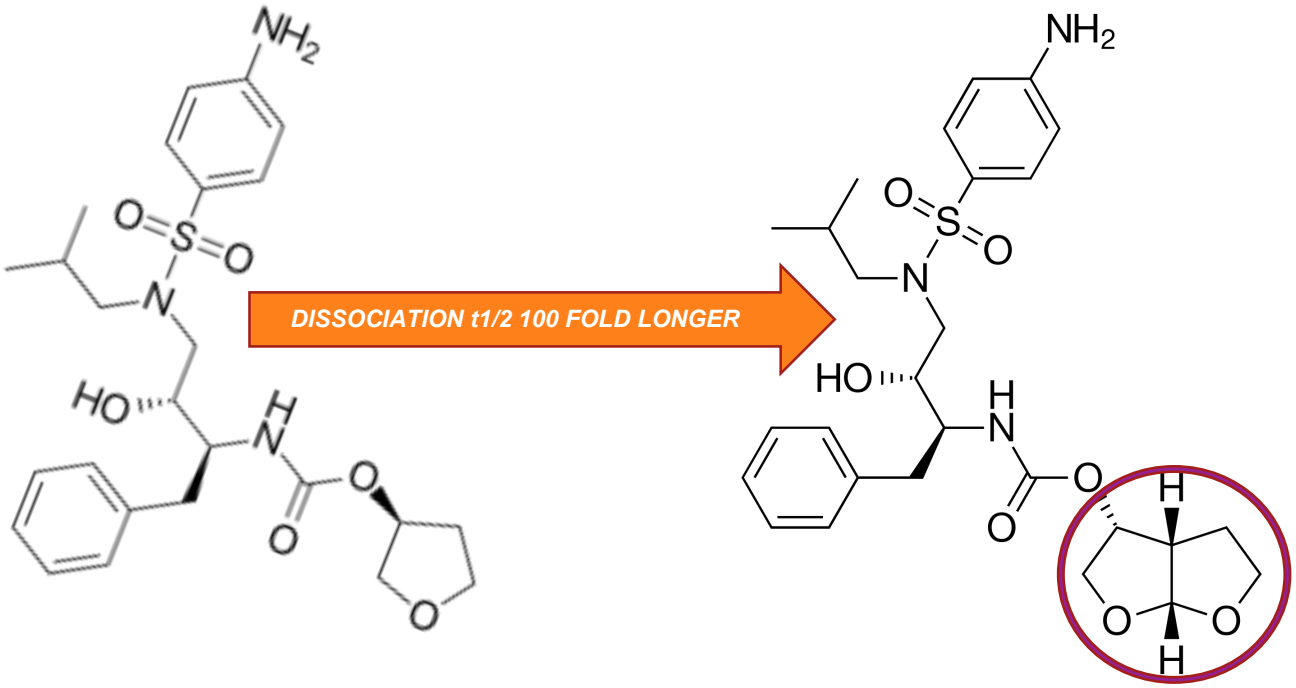
BIC

Halogenated Phenyl group:

- Interacts with the integrase pocket that is normally occupied by the terminal 3' base of viral DNA
- Improves the solubility molecule

1. Lazerwith SE, et al. ASM 2016. Boston, MA. Poster #414.
2. Tsiang M, et al. ASM 2016. Boston, MA. Poster #416
3. Tebbens JD , et al. Int. J. Mol. Sci. 2018, 19, 1785; doi:10.3390/ijms19061785

WE'VE SEEN THIS PHENOMENON BEFORE



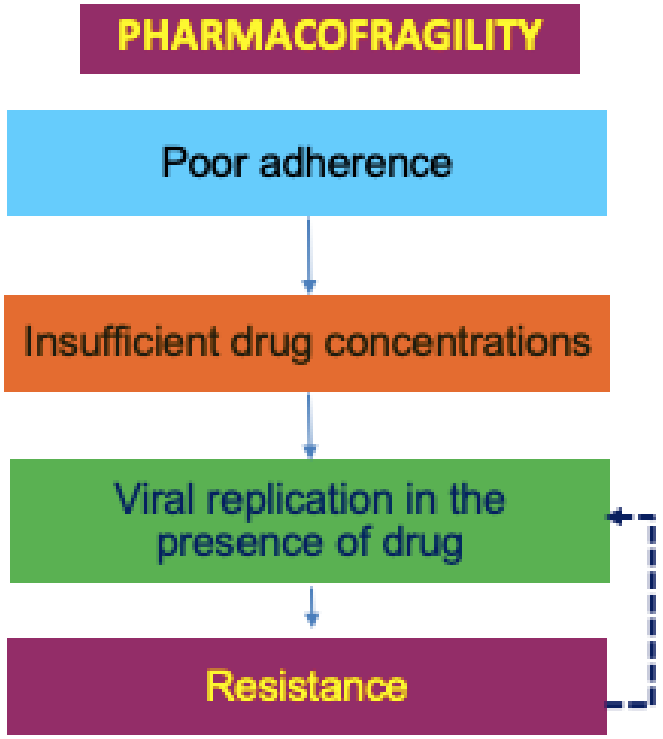
AMPRENAVIR **DARUNAVIR**

J Virol. 2007 Dec; 81(24): 13845–13851. PMCID: PMC2168871
Published online 2007 Oct 10. doi: 10.1128/JVI.01184-07 PMID: 17928344

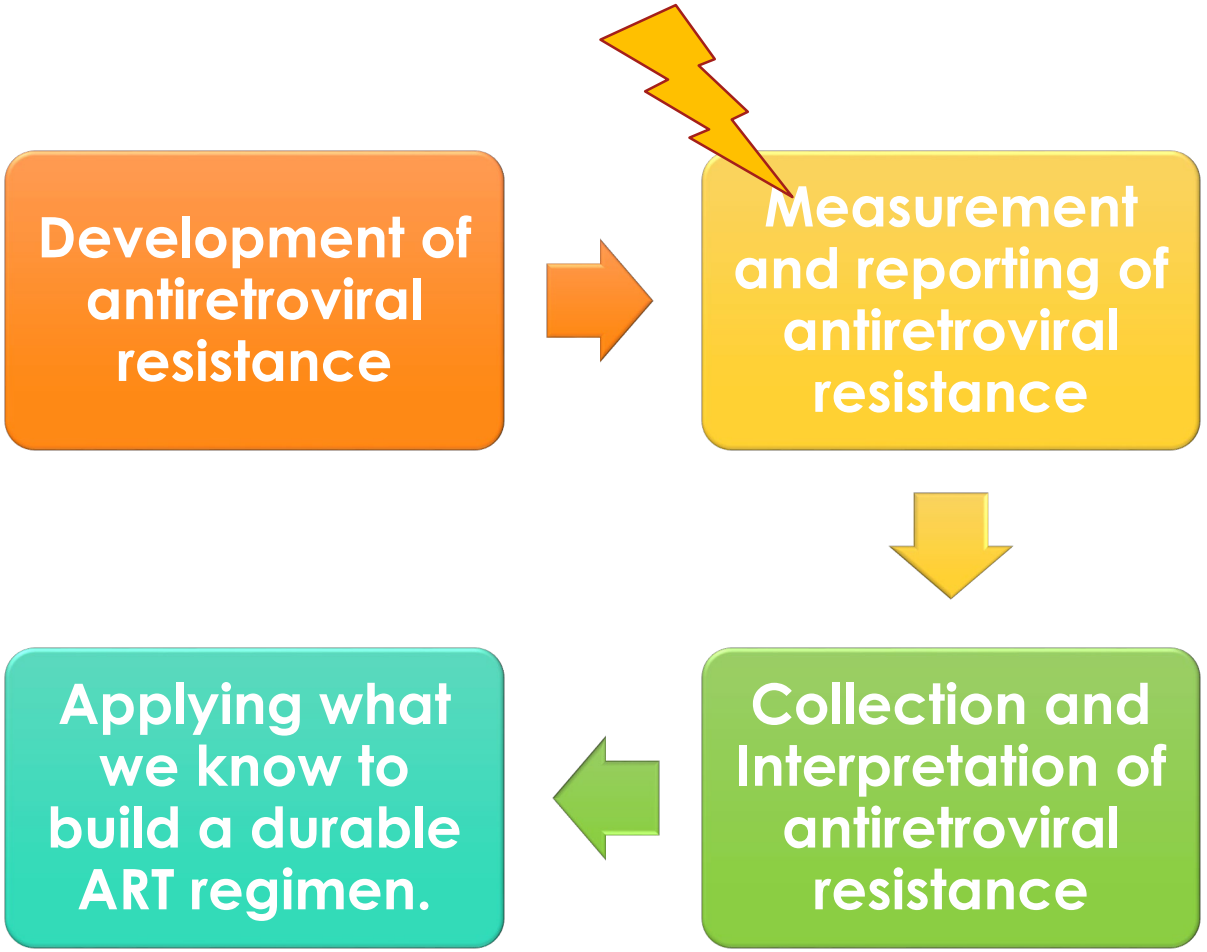
Binding Kinetics of Darunavir to Human Immunodeficiency Virus Type 1 Protease Explain the Potent Antiviral Activity and High Genetic Barrier

Inge Dierynck,* Mieke De Wit, Emmanuel Gustin, Inge Keuleers, Johan Vandersmissen, Sabine Hallenberger, and Kurt Hertogs

PHARMACOFRAGILITY SIMPLY…



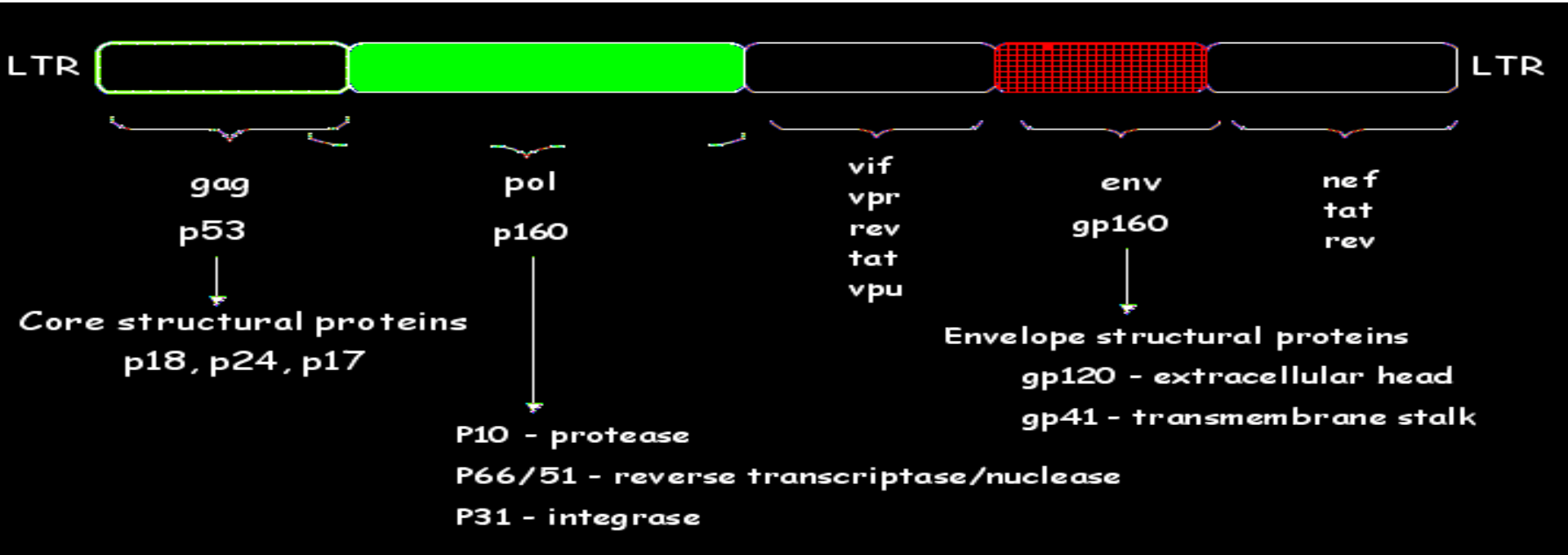
LEARNING OBJECTIVES



RESISTANCE ASSAYS

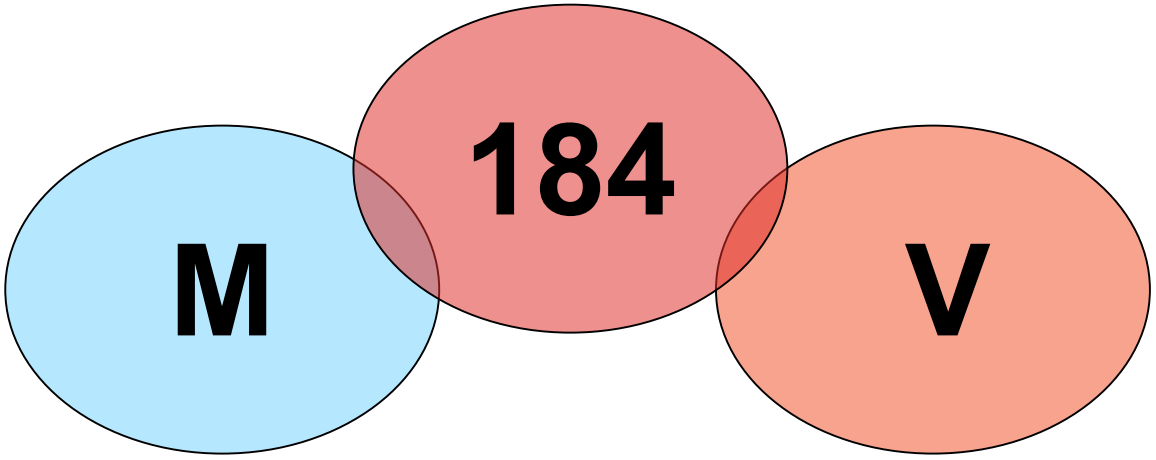
Genotype:

Looks at the **structure** of the HIV genome and detects changes in the section that codes for RT and Protease by sequencing viral RNA



REPORTING MUTATIONS

RT position 184



Methionine
(AUG)

Valine
(GUG)

	DRUGS		FOLD CHANGE [1]	CUT-OFF [2]		RESISTANCE ANALYSIS [3]	CLINICAL NOTES (see p2 for details)
	NRTI / NtRTI mutations: 41L, 44D, 67N, 75M, 118I, 184V, 208Y, 210W, 211wt/K, 214F, 215Y, 218E, 219N						
NRTI/NtRTI	Retrovir®	Zidovudine	12.6	1.2	9.6	MINIMAL RESPONSE	
	Epivir®	Lamivudine	46.0	1.0	3.4	MINIMAL RESPONSE	
	Videx®	Didanosine	2.1	0.9	2.6	REDUCED RESPONSE	
	Zerit®	Stavudine	1.9	0.9	2.0	REDUCED RESPONSE	
	Ziagen®	Abacavir	4.9	0.8	1.9	MINIMAL RESPONSE	
	Emtriva®	Emtricitabine	43.1	3.5		RESISTANT	
	Viread®	Tenofovir DF	2.3	0.9	2.1	MINIMAL RESPONSE	
	NNRTI mutations: 98S, 103N						
NNRTI	Viramune®	Nevirapine	53.3	5.5		RESISTANT	
	Sustiva® , Stocrin®	Efavirenz	11.8	3.4		RESISTANT	
	PI mutations: 10I, 15V, 20R, 35D, 36I, 37D, 46L, 53L, 54V, 55R, 58E, 62V, 63P, 71V, 73T, 82A, 90M						
PI	Crixivan®	Indinavir	119.8	0.9	4.5	MINIMAL RESPONSE	
	Crixivan ®; boosted	Indinavir/r	119.8	10.6	40.1	MINIMAL RESPONSE	
	Viracept®	Nelfinavir	55.1	1.3	7.3	MINIMAL RESPONSE	
	Invirase®; boosted	Saquinavir/r	138.8	7.1	26.5	MINIMAL RESPONSE	
	Lexiva®,Telzir®; boosted	Fosamprenavir/r	9.3	1.3	11.4	REDUCED RESPONSE	
	Kaletra®	Lopinavir/r	105.0	9.7	56.1	MINIMAL RESPONSE	
	Reyataz®; boosted	Atazanavir/r	103.6	2.7	32.9	MINIMAL RESPONSE	
	Aptivus®; boosted	Tipranavir/r	2.8	1.2	5.4	REDUCED RESPONSE	Note 1
	Prezista™; boosted	Darunavir/r	2.4	3.4	96.9	MAXIMAL RESPONSE	Note 2

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Patient ID:	17N0078275	**Sample Date:**	21-Mar-2017
Secondary ID:		**Study ID:**	DRT
Birthdate:	09-Sep-1955	**Report Date:**	10-Apr-2017
		Clade:	C

NRTI/NtRTI Drugs	Fold Change[1]	Cut-off[2]		Resistance Analysis[3]
Zidovudine (Retrovir)	1.5	1.5	11.4	SUSCEPTIBLE
Lamivudine (Epivir)	44.2	2.1	4.6	RESISTANT
Didanosine (Videx)	1.4	0.9	2.6	REDUCED RESPONSE
Stavudine (Zerit)	0.7	1.0	2.3	SUSCEPTIBLE
Abacavir (Ziagen)	2.4	0.9	3.5	REDUCED RESPONSE
Emtricitabine (Emtriva)	38.7	3.1		RESISTANT
Tenofovir (Viread)	0.7	1.0	2.3	SUSCEPTIBLE
NRTI/NtRTI Mutations[4]: 184V, 215N/S/wt/Y				

NNRTI Drugs	Fold Change[1]	Cut-off[2]		Resistance Analysis[3]
Nevirapine (Viramune)	80.6	6.0		RESISTANT
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Etravirine (Intelence)	6.4	3.2	27.6	REDUCED RESPONSE
Rilpivirine (Endurant)	11.9	3.1		RESISTANT
NNRTI Mutations[4]: 103N, 108I/wt, 138A, 225H				

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Saquinavir/r (Invirase)	0.7	3.1	22.6	SUSCEPTIBLE
Fosamprenavir/r (Lexiva, Telzir)	0.7	1.5	19.5	SUSCEPTIBLE
Lopinavir/r (Kaletra)	0.6	6.1	51.2	SUSCEPTIBLE
Atazanavir/r (Reyataz)	0.9	2.5	32.5	SUSCEPTIBLE
Tipranavir/r (Aptivus)	0.8	1.5	7.0	SUSCEPTIBLE
Darunavir/r (Prezista)	0.5	10.0	106.9	SUSCEPTIBLE
PI Mutations[4]: 74S				

RESISTANCE ASSAYS

Phenotype:

Looks at the **function** of the HIV and measures its ability to grow in different concentrations of antiretroviral drugs.

TACKLING ART RESISTANCE

MANAGEMENT OF TREATMENT EXPERIENCED HIV PART 2

Linda Robinson BSc.Phm, AAHIVP

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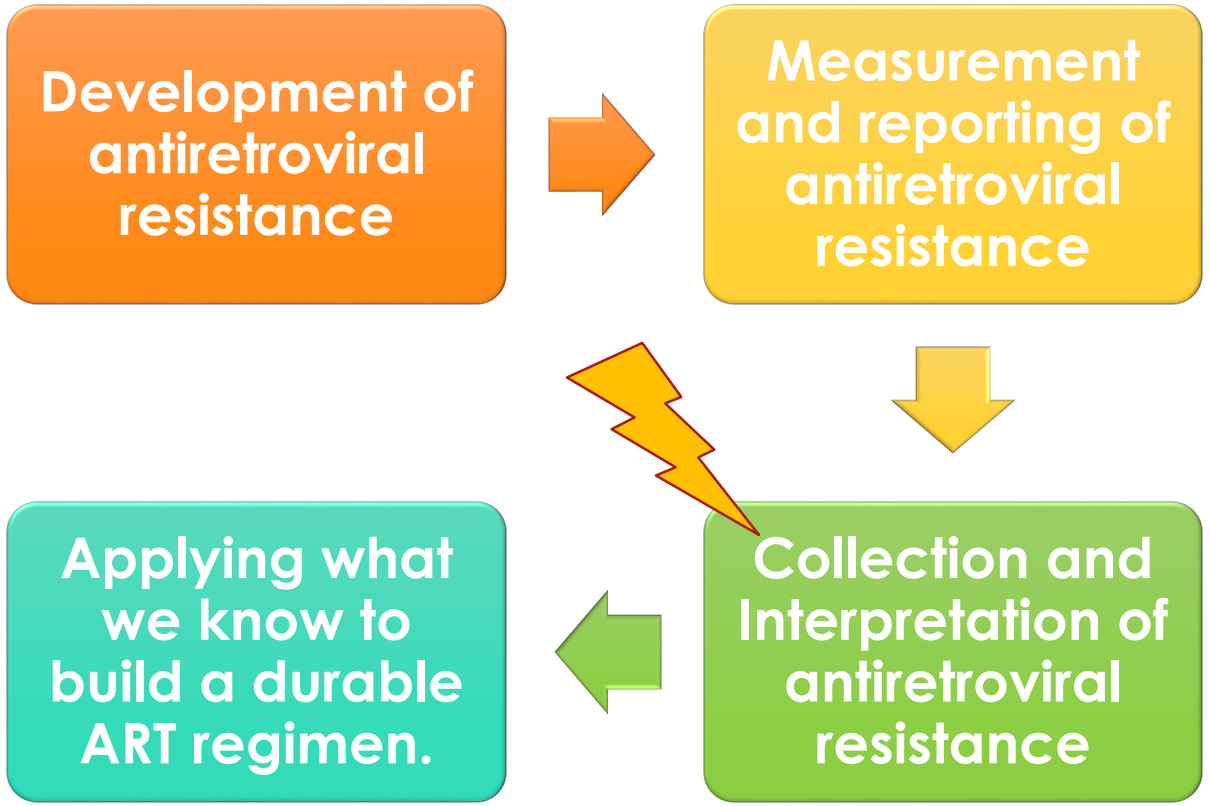
Past-Chair CHAP: 2013 & 2021

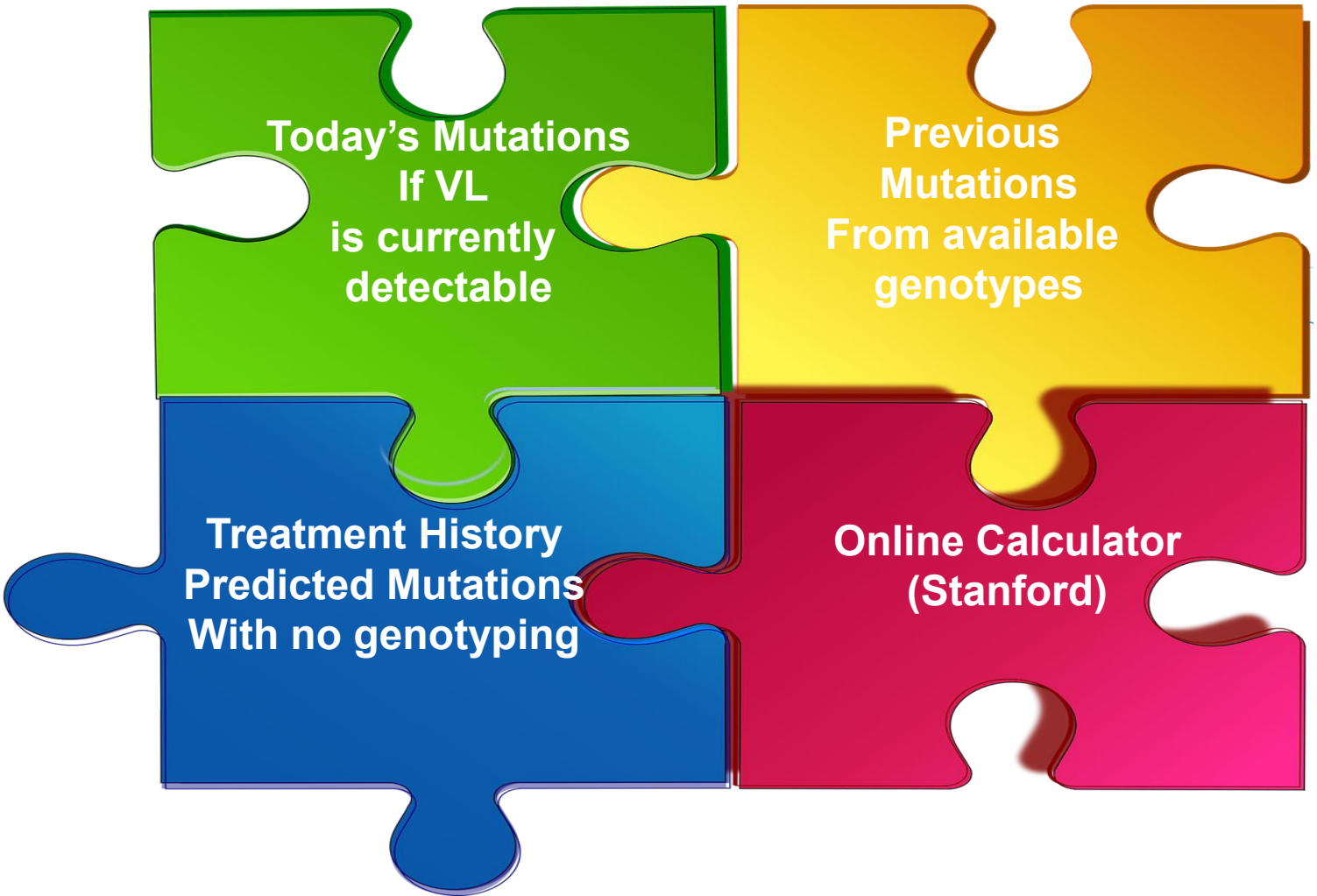
LEARNING OBJECTIVES



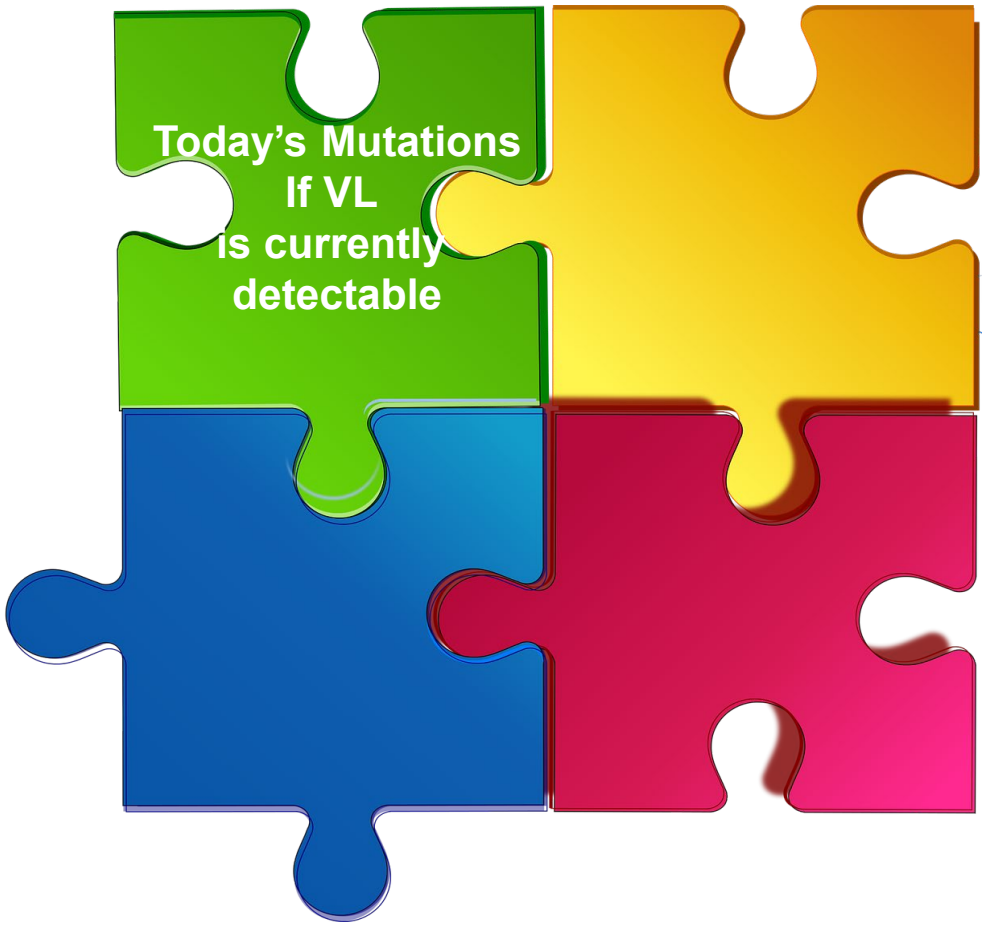
A CASE EXAMPLE

- HIV+ve x 30 years
- On 6th regimen
- RTV Boosted Darunavir BID and Raltegravir BID and Etravirine BID
- Has been undetectable on this regimen for 8 years
- Asks if you can give him once daily regimen and less pills

BUILDING THE BEST ART REGIMEN IS AS EASY AS BUILDING A PUZZLE



RESISTANCE TODAY



- He is currently undetectable
- Not only can we not do a genotype because we need enough virus to grow……
- We can also assume that there is activity from the current combination and doses of drugs because they are suppressing his virus

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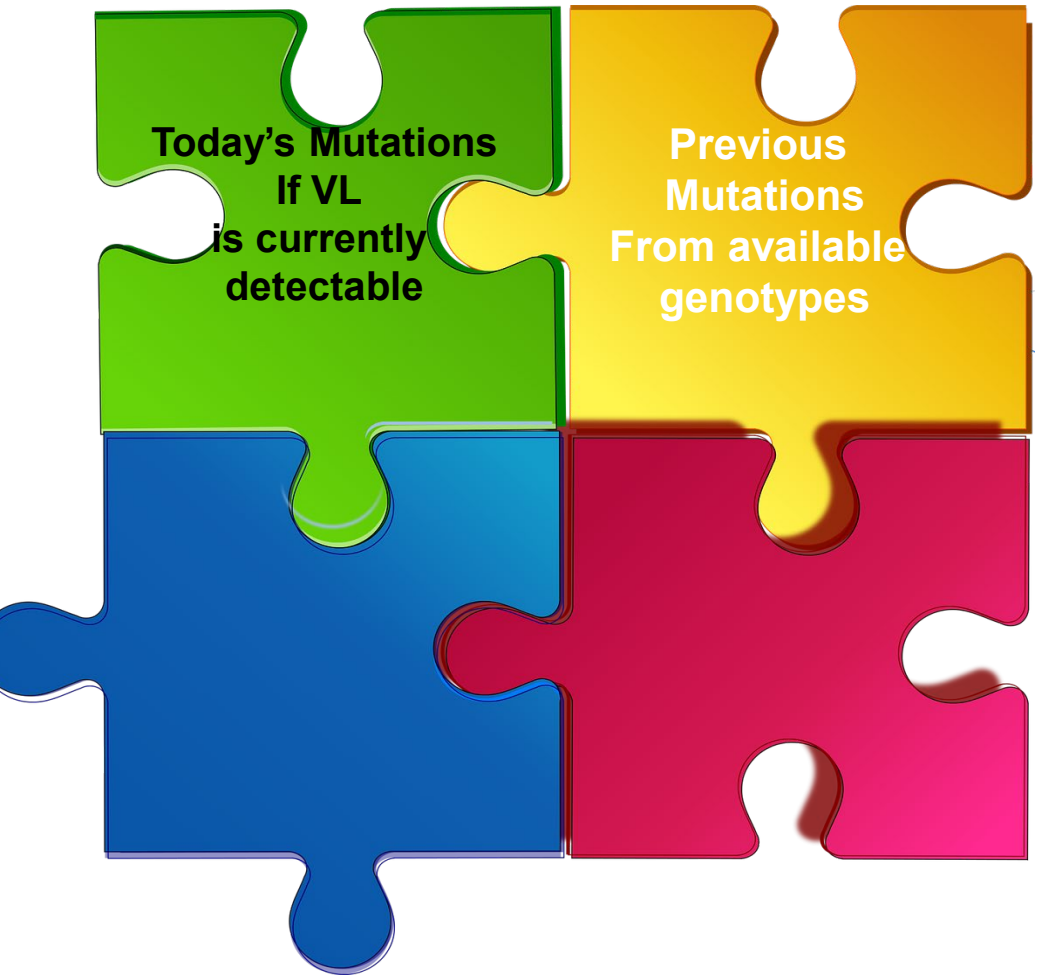
ARCHIVED RESISTANCE



- 2000 NVP + DDI + D4T
  - RT 181C, 74V, 67N
- 2002 NFV + DDI + ABC
  - PI 30N, 90M
  - RT 74V, 44D, 65R
- 2003 IDV/r + DDI + TDF
  - PI 82A
  - RT same
- 2007 LPV/r + TDF + AZT
  - PI (none)
  - RT 41L, 215Y

BC GENOTYPE LABORATORY

General Information

Confidentiality BC-CfE laboratory test results, like other laboratory results, are kept strictly confidential.

Turnaround Time BC-CfE laboratory test results are usually available within 2 weeks (after samples received from other clinical laboratories).

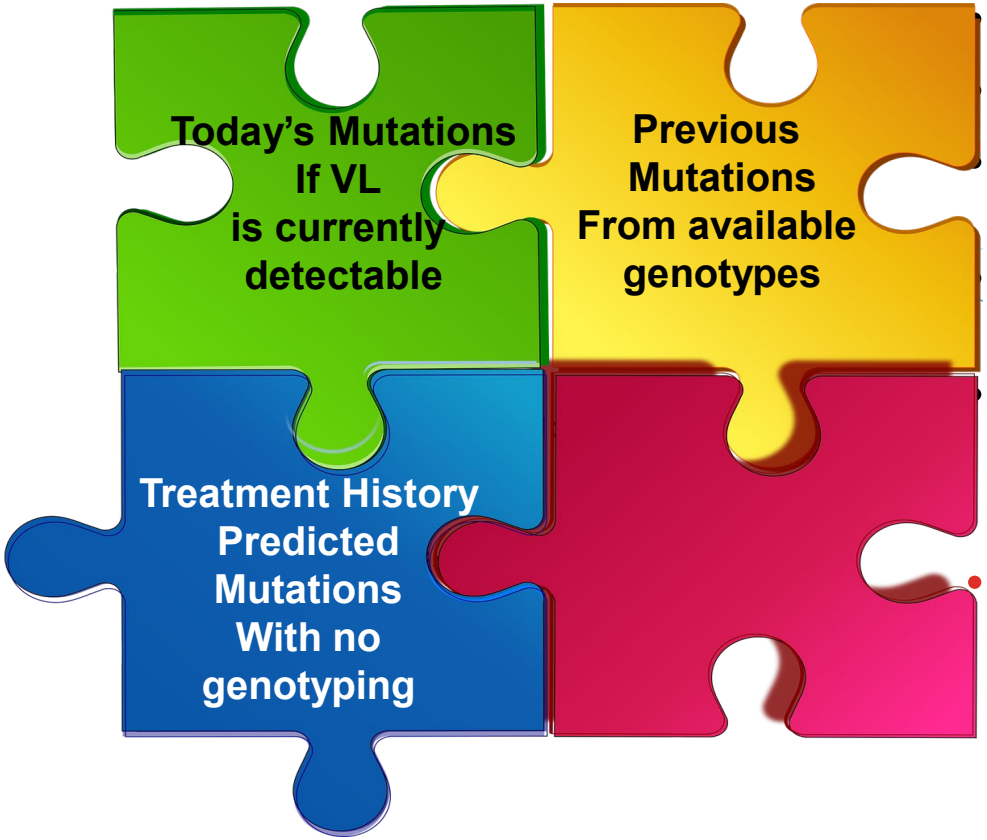
Specimen collection and handling instructions: See Laboratory Test Order Forms

Who can I contact if I have any questions? If you have any questions, please contact us at 1-800-517-1119 during business hours (9 AM to 5 PM PST).

Suggestions concerns, compliments and complaints can be emailed to lab@bccfe.ca

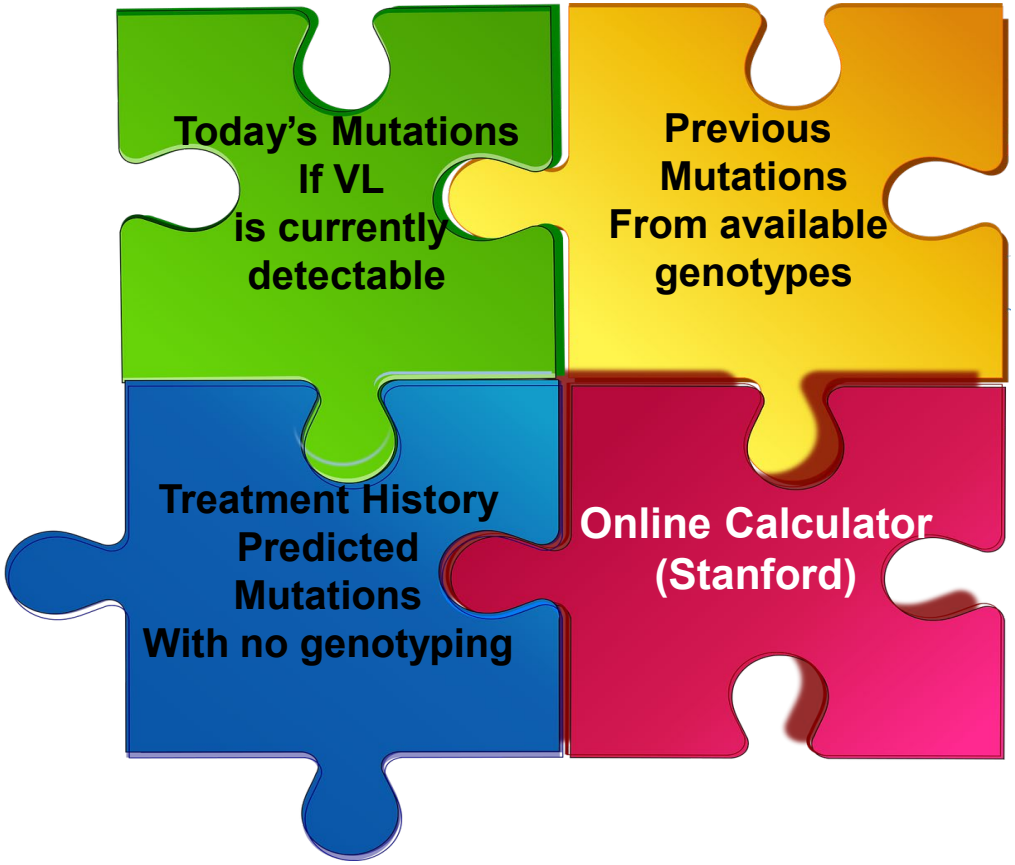
1-800-517-1119

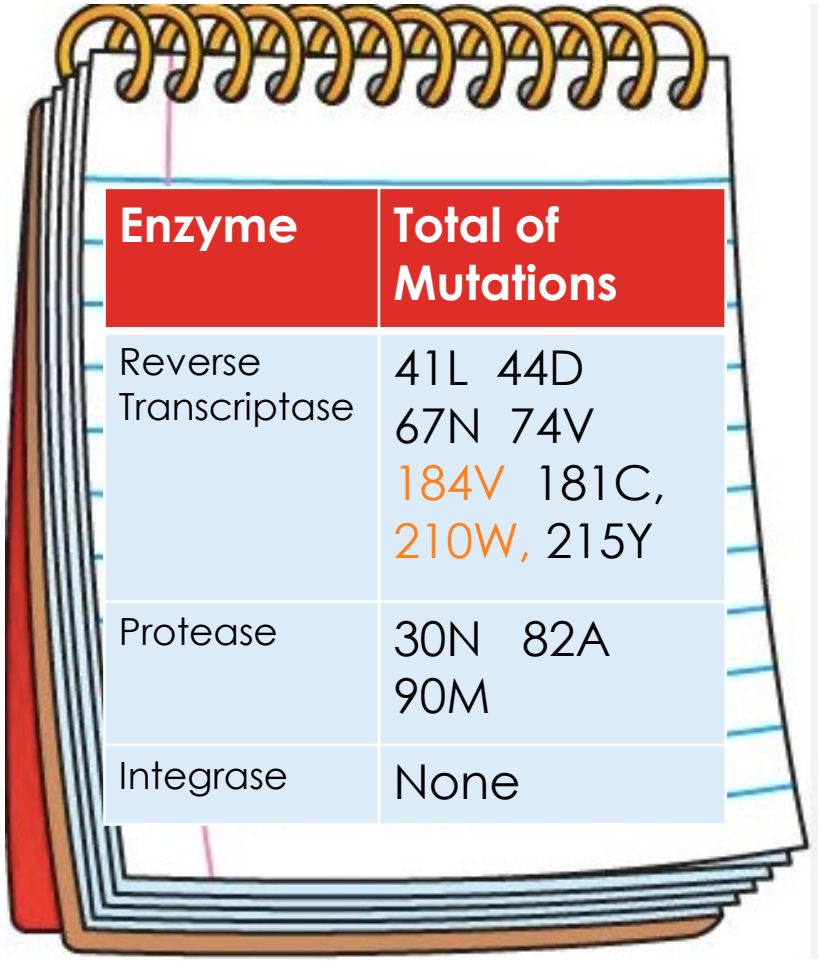
PREDICTED RESISTANCE



- Positive x 30 years
- = Diagnosis in 1994!
- Triple Therapy not available until 1995.
- Genotypes not available until 1999!
- History reveals Dual therapy with AZT/3TC
- **Prediction? … 184 V and any missing TAMS (210W)**

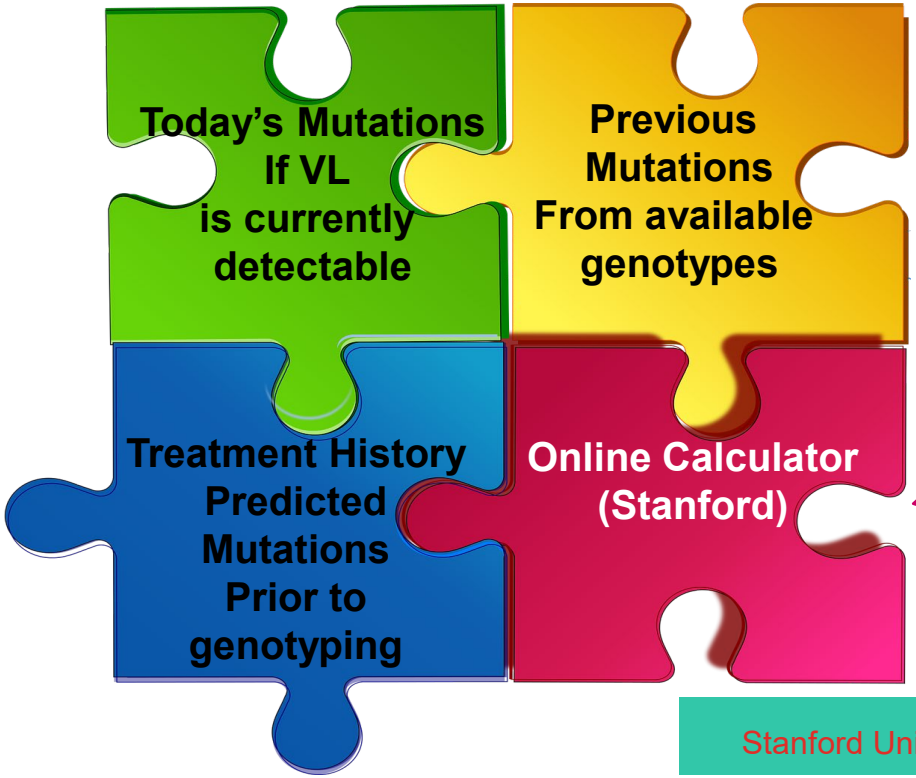
PUTTING THE PIECES TOGETHER





Enzyme	Total of Mutations
Reverse Transcriptase	41L 44D 67N 74V 184V 181C, 210W, 215Y
Protease	30N 82A 90M
Integrase	None

RESISTANCE MUTATIONS ARE A KEY CONSIDERATION IN BUILDING DURABLE ART REGIMENS

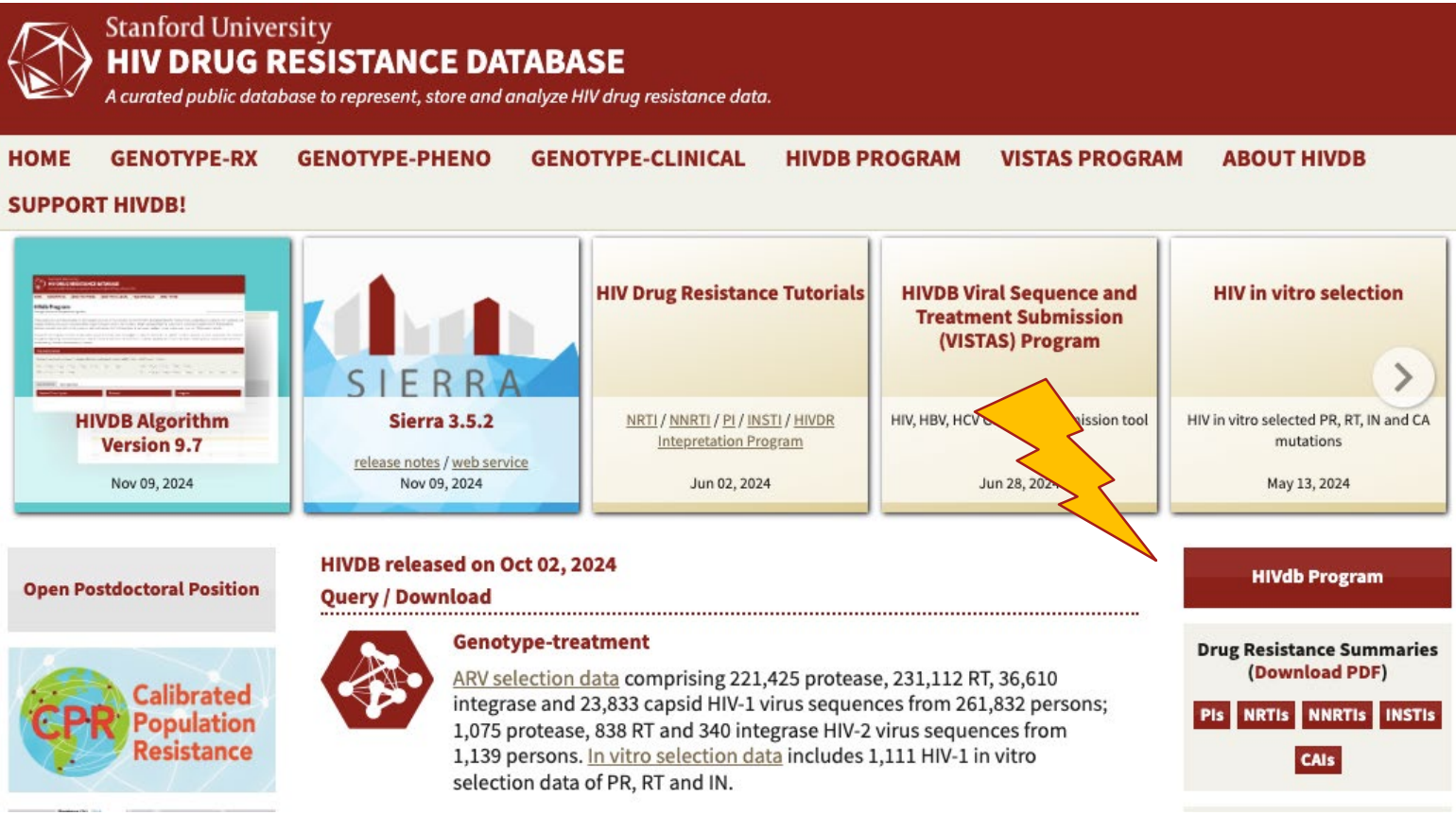


Stanford University HIV Drug Resistance Database

- Allows one to enter either a mutation list or a sequence
- Offers an on-line analysis, comparison and report from 3 reputable, world-known algorithms

Stanford University HIV Drug Resistance Database http://hivdb.stanford.edu/

SEARCH: HIVDB


Stanford University
HIV DRUG RESISTANCE DATABASE
A curated public database to represent, store and analyze HIV drug resistance data.
HOME
GENOTYPE-RX
GENOTYPE-PHENO
GENOTYPE-CLINICAL
HIVDB PROGRAM
VISTAS PROGRAM
ABOUT HIVDB
SUPPORT HIVDB!
HIVDB Algorithm Version 9.7
Nov 09, 2024
SIERRA
Sierra 3.5.2
release notes / web service
Nov 09, 2024
HIV Drug Resistance Tutorials
NRTI / NNRTI / PI / INSTI / HIVDR Intepretation Program
Jun 02, 2024
HIVDB Viral Sequence and Treatment Submission (VISTAS) Program
HIV, HBV, HCV
Jun 28, 2024
HIV in vitro selection
HIV in vitro selected PR, RT, IN and CA mutations
May 13, 2024
Open Postdoctoral Position
CPR Calibrated Population Resistance
HIVDB released on Oct 02, 2024
Query / Download
Genotype-treatment
ARV selection data comprising 221,425 protease, 231,112 RT, 36,610 integrase and 23,833 capsid HIV-1 virus sequences from 261,832 persons; 1,075 protease, 838 RT and 340 integrase HIV-2 virus sequences from 1,139 persons. In vitro selection data includes 1,111 HIV-1 in vitro selection data of PR, RT and IN.
HIVdb Program
Drug Resistance Summaries (Download PDF)
PIs
NRTIs
NNRTIs
INSTIs
CAIs

Stanford University
HIV DRUG RESISTANCE DATABASE
A curated public database to represent, store and analyze HIV drug resistance data.

HOME GENOTYPE-RX GENOTYPE-PHENO GENOTYPE-CLINICAL HIVDB PROGRAM VISTAS PROGRAM ABOUT HIVDB
SUPPORT HIVDB!

HIVdb Program: Mutations Analysis

HIVdb accepts user-submitted protease, RT, and integrase sequences or mutations and returns inferred levels of resistance to the most commonly used protease, nucleoside, non-nucleoside, and integrase inhibitors. Its purpose is educational and as such it provides extensive comments and a highly transparent scoring system that is hyperlinked to data in the HIV Drug Resistance Database. A detailed description of the program as well as all updates is in the Release Notes. A web service has been created to allow users to access HIVdb programmatically.

New: this program is now available for analyzing SARS-CoV-2 mutations, FASTA, and FASTQ (NGS) sequences.

Protease, RT, and integrase mutations can be entered using either the text box or auto-suggestion boxes. To use the text box, type each mutation separated by one or more spaces. The consensus wildtype and separating commas are optional. If there is a mixture of more than one amino acid at a position, write both amino amino acids (an intervening slash is optional). Insertions should be indicated by "Insertion" and deletions by "Deletion".

Drug display options

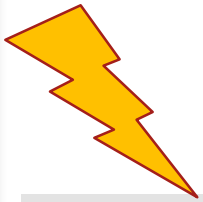
By default, results will be shown for checked ARVs. Use checkboxes for additional ARVs. (select all ARVs, revert to default)

NRTI: ☑ ABC ☑ AZT ☑ FTC ☑ 3TC ☑ TDF ☐ D4T ☐ DDI

NNRTI: ☑ DOR ☑ EFV ☑ ETR ☑ NVP ☑ RPV

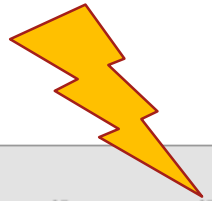
INSTI: ☑ BIC ☑ CAB ☑ DTG ☑ EVG ☑ RAL

PI: ☑ ATV/r ☑ DRV/r ☑ LPV/r ☐ FPV/r ☐ IDV/r ☐ NFV ☐ SQV/r ☐ TPV/r



Reverse Transcriptase

Enter/paste mutations



40	41	44	62	65	67	68	69	70	74	75
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77	90	98	100	101	103	106	108	115	116	118
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138	151	179	181	184	188	190	210	215	219	221
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225	227	230	234	236	238	318	348
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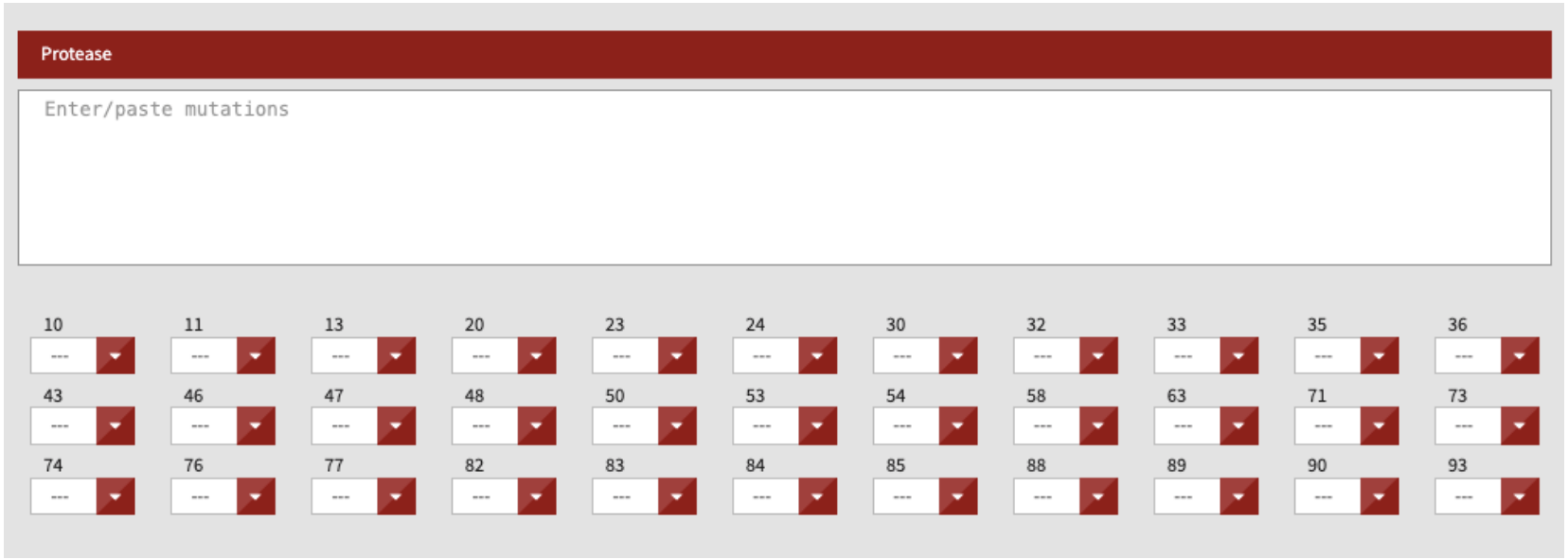
Protease
Enter/paste mutations
10
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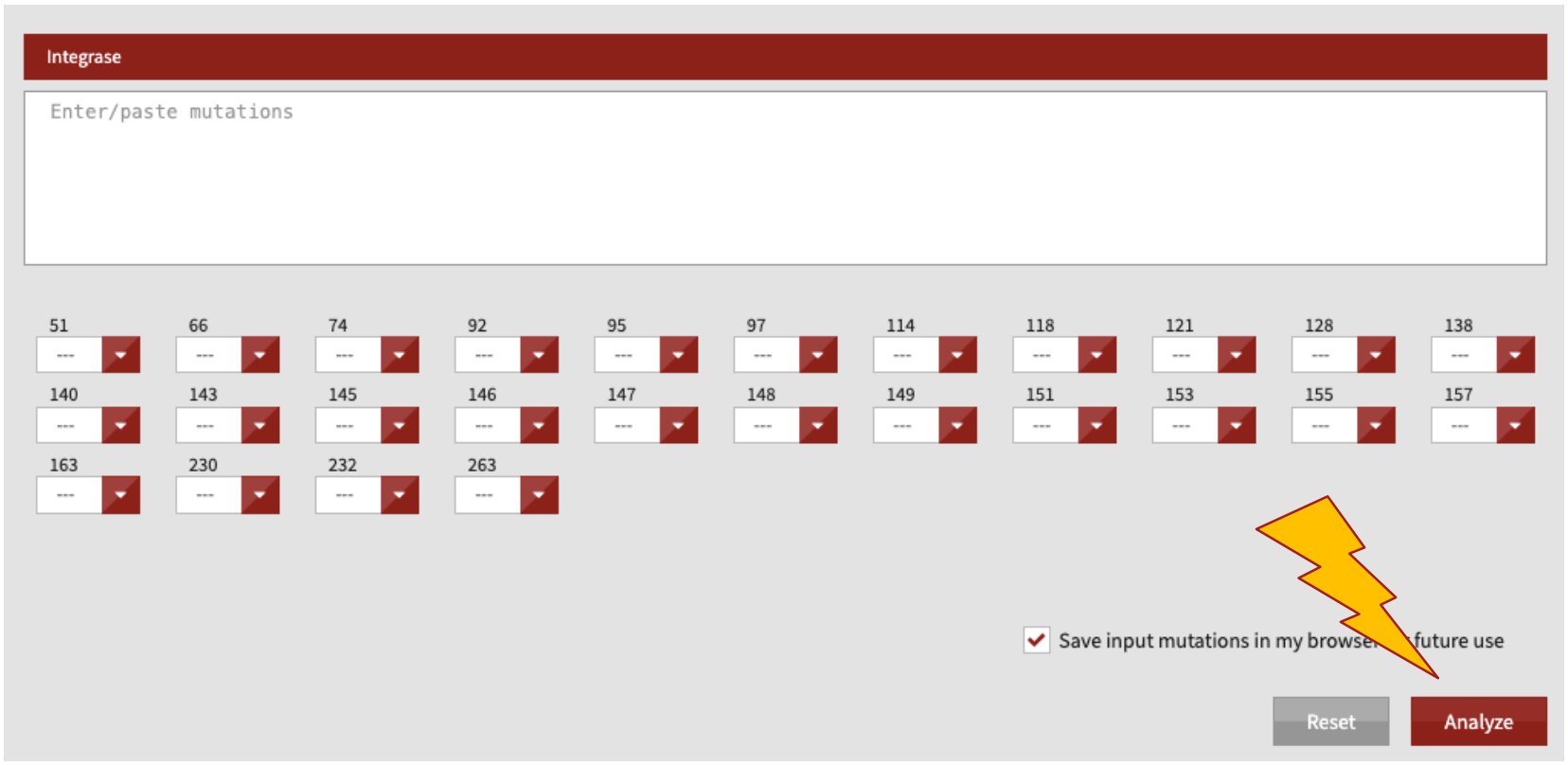
Integrase
Enter/paste mutations
51
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74
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128
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140
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147
148
149
151
153
155
157
163
230
232
263
Save input mutations in my browser
future use
Reset
Analyze

Drug resistance interpretation: PR — HIVDB 9.7 (2024-11-09)

PI Major Mutations:	D30N · V82A · L90M
PI Accessory Mutations:	None
PR Other Mutations:	None

Protease Inhibitors	
atazanavir/r (ATV/r)	Intermediate Resistance
darunavir/r (DRV/r)	Susceptible
lopinavir/r (LPV/r)	Intermediate Resistance

PR comments

Major

- **D30N** is a non-polymorphic mutation NFV-selected mutation that causes high-level resistance to NFV but not to other PIs.
- **V82A** is a non-polymorphic mutation selected primarily by IDV and LPV. It is associated with reduced susceptibility to LPV and to a lesser extent ATV. It increases DRV susceptibility.
- **L90M** is a non-polymorphic PI-selected mutation that reduces susceptibility to ATV and to a lesser extent LPV.

Drug resistance interpretation: RT — HIVDB 9.7 (2024-11-09)

NRTI Mutations:	M41L · E44D · D67N · L74V · M184V · L210W · T215Y
NNRTI Mutations:	Y181C
RT Other Mutations:	None

Nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	High-Level Resistance
zidovudine (AZT)	High-Level Resistance
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	High-Level Resistance

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

RT comments

NRTI

- **M41L** is a TAM that usually occurs with T215Y. In combination, **M41L** plus T215Y confer intermediate / high-level resistance to AZT and d4T and contribute to reduced ddI, ABC and TDF susceptibility.
- **E44D** is a relatively non-polymorphic accessory mutation; E44A is a nonpolymorphic accessory mutation. Each usually occurs with multiple TAMs.
- **D67N** is a non-polymorphic TAM associated with low-level resistance to AZT.
- **L74V** causes intermediate ABC resistance. L74I causes low-level ABC resistance.
- **M184V/I** cause high-level in vitro resistance to 3TC and FTC and low/intermediate resistance to ABC (3-fold reduced susceptibility). **M184V/I** are not contraindications to continued treatment with 3TC or FTC because they increase susceptibility to AZT and TDF and are associated with clinically significant reductions in HIV-1 replication.
- **L210W** is a TAM that usually occurs in combination with M41L and T215Y. The combination of M41, **L210W** and T215Y causes high-level resistance to AZT and intermediate resistance to ABC and TDF.
- **T215Y/F** are TAMs that causes intermediate/high-level resistance to AZT and potentially low-level resistance to ABC and TDF.

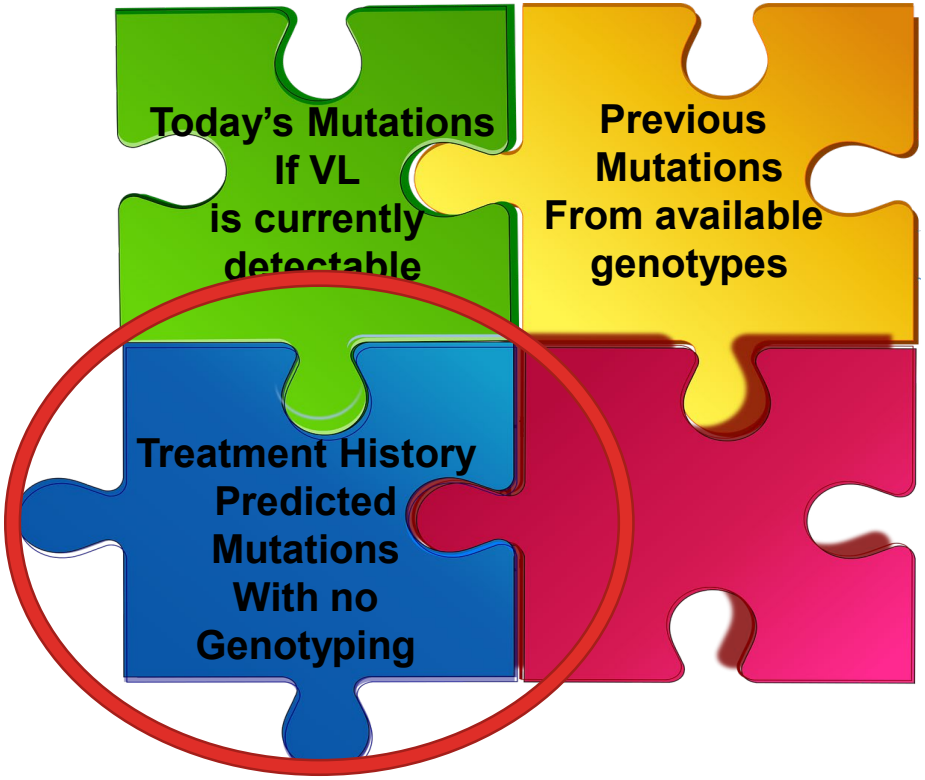
NNRTI

- **Y181C** is a non-polymorphic mutation selected in persons receiving NVP, ETR and RPV. It confers high-level resistance to NVP, intermediate resistance to ETR and RPV, and low-level resistance to EFV. Alone, it does not significantly reduce DOR susceptibility.

Dosage

- This virus is predicted to have intermediate-level reduced susceptibility to **RPV**. The use of the combination of CAB/**RPV** should be considered to be contraindicated.

PREDICTED RESISTANCE



- Positive x 30 years
- = Diagnosis in 1994!
- Triple Therapy not available until 1995.
- Genotypes not available until 1999!
- History reveals Dual therapy with AZT/3TC

- **Prediction? … 184 V and any missing TAMS (210W)**

BUT WHY AND HOW DO I KNOW THIS?

TACKLING ART RESISTANCE

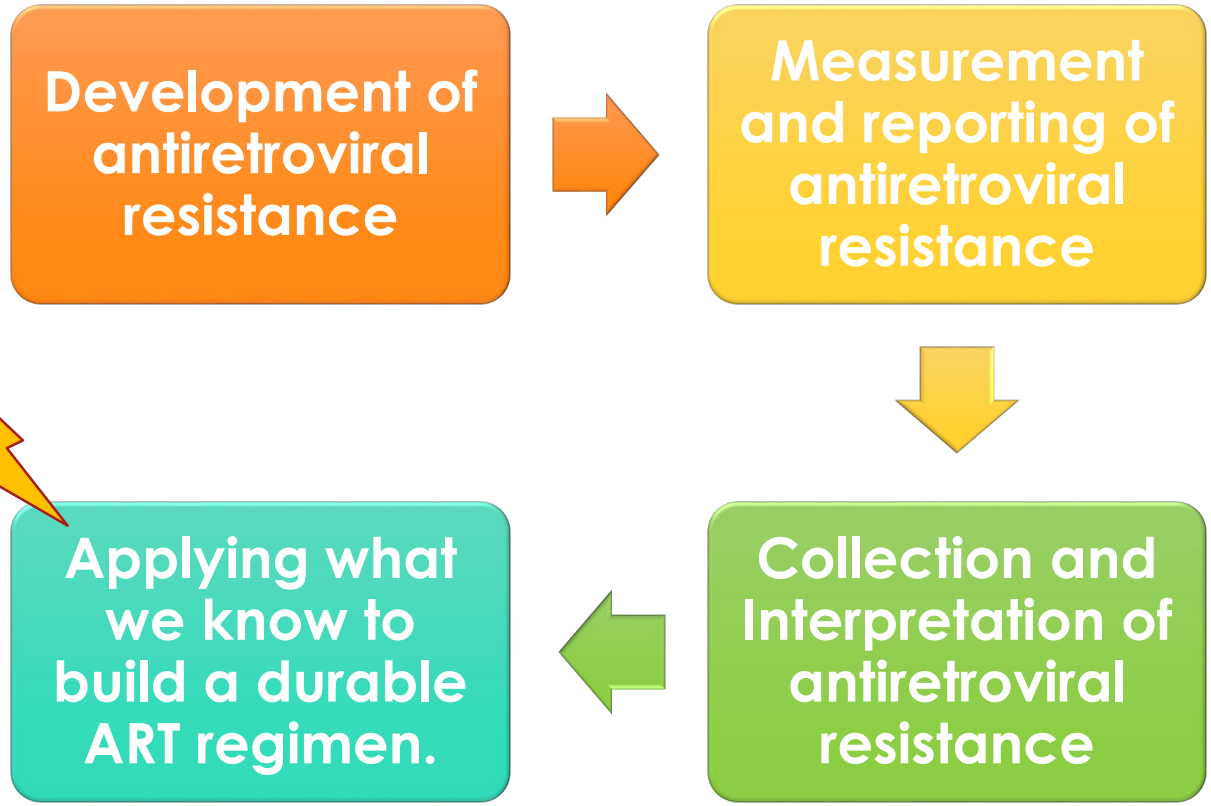
MANAGEMENT OF TREATMENT EXPERIENCED HIV PART 3

Linda Robinson BSc.Phm, AAHIVP

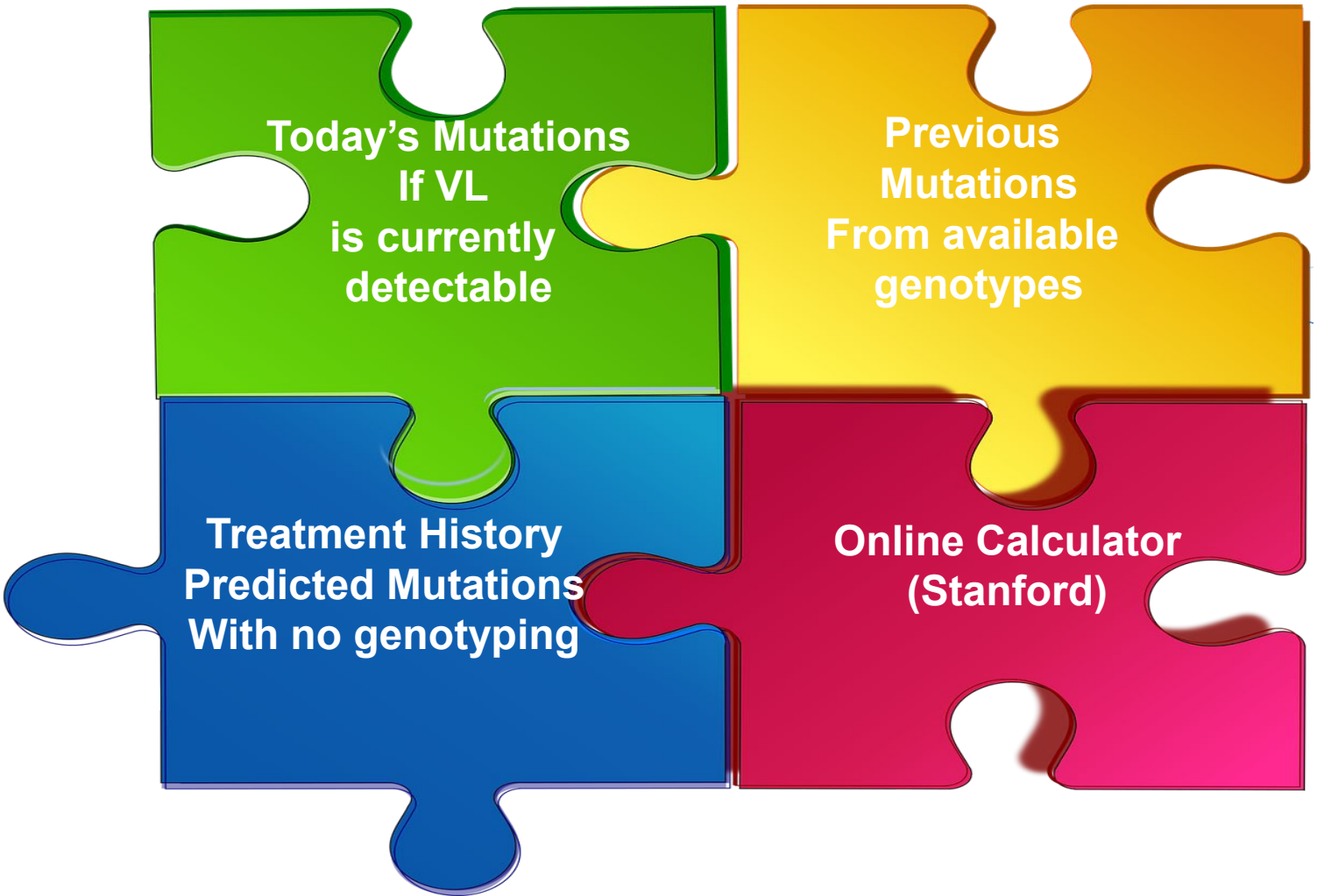
HIV Pharmacotherapy Specialist

Past-Chair CHAP: 2013 & 2021

LEARNING OBJECTIVES



IF YOU CAN BUILD THIS PUZZLE YOU CAN BUILD THE BEST ART REGIMEN



RESISTANCE MUTATIONS & PATHWAYS

From AZT to DTG

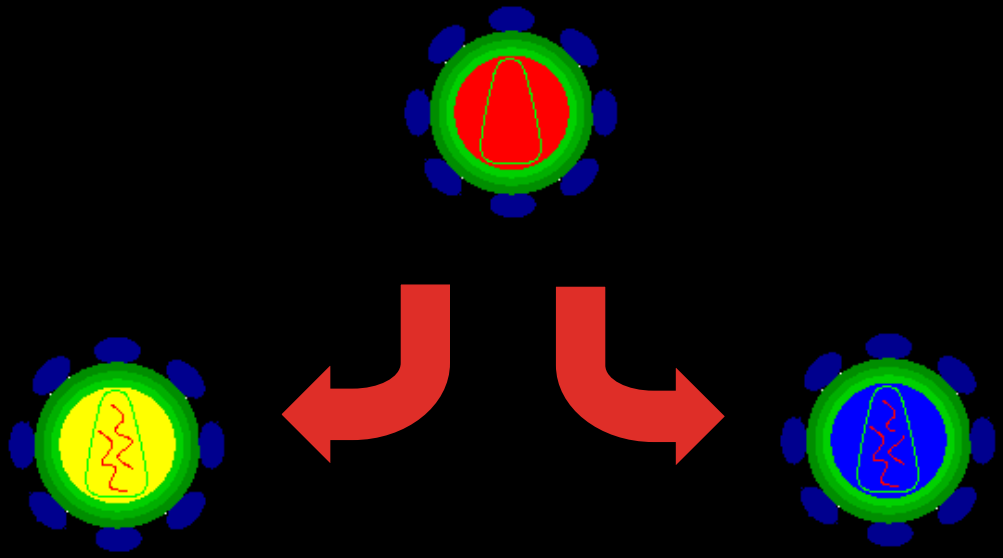
TAMS (NAMS)

Thymidine Analogue Mutations are actually a subset of a larger group of mutations called the NAMS, or Nucleoside Analogue Mutations.

- TAMS evolve under the pressure of AZT and d4T and can alone or in combination with other NAMS confer cross resistance to all NRTI's.

TAM PATHWAYS

AZT or d4T



210W
41L
215Y

67N
70R
219Q

TAM Pathway 1

TAM Pathway 2

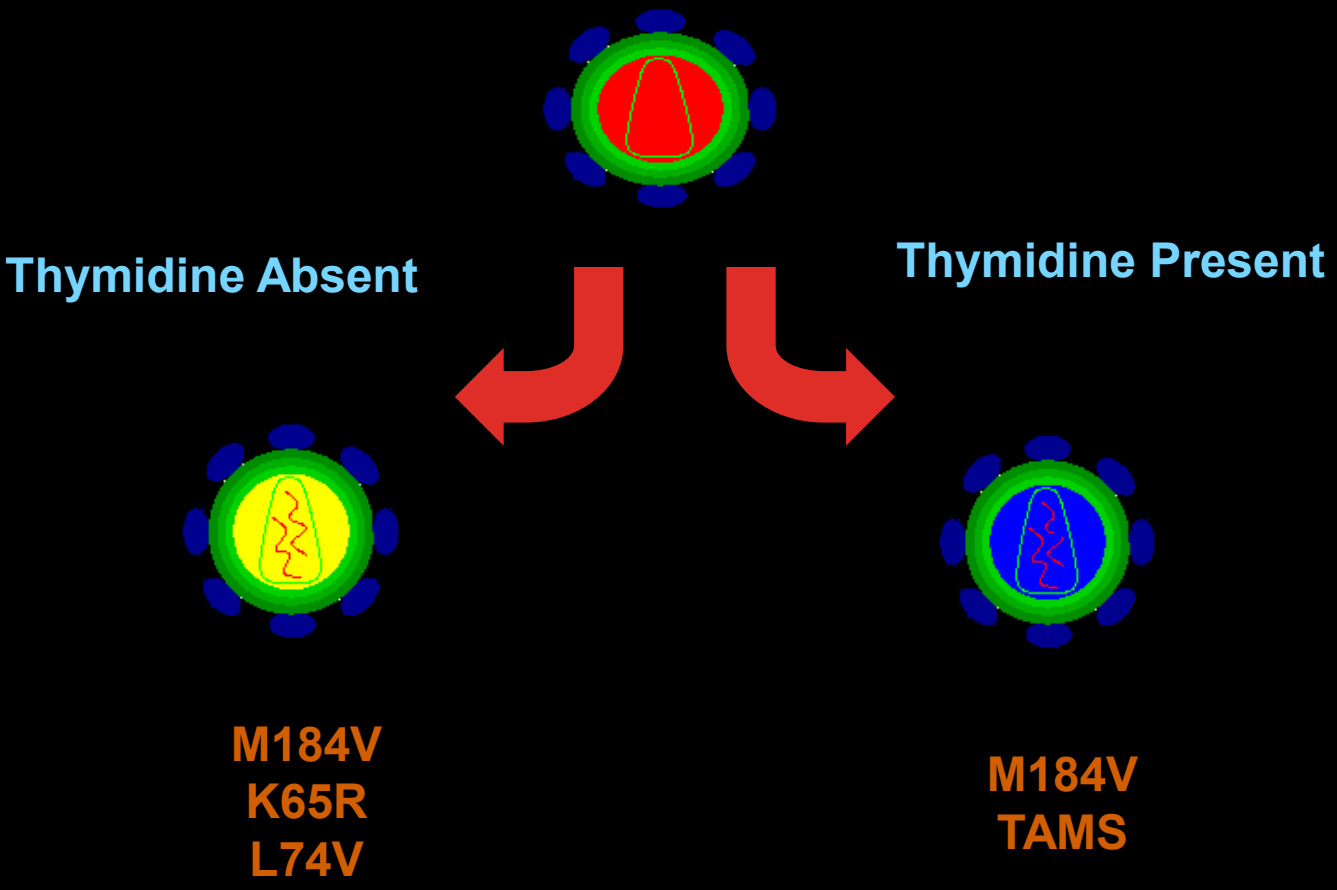
TAM PATHWAY 1: 210W, 41L, 215Y

- Confers higher levels of resistance to zidovudine
- Confer more cross-resistance to other NRTI's including tenofovir
- Virus with this pathway will not become resensitized to zidovudine in the presence of M184V
- 3 or more TAMS that include 210W may reduce susceptibility to tenofovir

TAM PATHWAY 2: 67N, 70R, 219Q

- Confer lower levels of resistance to zidovudine
- Confer less cross-resistance to other NRTI's
- Virus with this mutation pattern may become resensitized to thymidine analogues in the presence of M184V
- Tenofovir remains active against viruses carrying the mutations in this pathway

ABACAVIR PATHWAYS



THE M184V MUTATION:

- Selected under the pressure of cytosine analogues, namely lamivudine (3TC), zalcitabine (ddC), emtricitabine (FTC) causing high level resistance to these
- Causes a modest reduction in susceptibility to abacavir and didanosine (ddI) on its own and more so in combination with other NAMs
- Virus can also select for this mutation under abacavir pressure

THE M184V MUTATION (CONT'D)

- Increases susceptibility to TFV, d4T, AZT
- May delay emergence of TAMS in AZT-treated patients
- Reduces TFV resistance caused by TAMS
- Maintenance of this mutation leads to a less fit virus and may reduce viral replicative capacity

THE L74V MUTATION

- Selected under abacavir and didanosine pressure
- Likely to occur with M184V in Kivexa failures.
- Rarely occurs with K65R in same isolate but may be a marker for it to come
- Causes:
    - Resistance to abacavir
    - Resistance to didanosine
    - Hypersusceptibility to zidovudine and tenofovir

THE K65R MUTATION

- Selected under pressure of abacavir, didanosine, tenofovir
- Causes resistance to didanosine, lamivudine, tenofovir and emtricitabine (FTC)
- M184V and K65R = loss to didanosine and abacavir
- Concomitant use of zidovudine with tenofovir may reduce emergence of K65R

THE K65R MUTATION: CLADE C

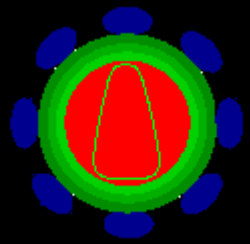
- Clade C Virus under inadequate pressure of NVP/d4T/3TC (Triomune) will most likely develop the K65R resistance mutation in RT
- This will confer high level resistance to all nukes currently available for second line therapy in most African centers where Clade C is prevalent

ADHERENCE AND ACCESS +++NB!!

SUMMARY OF NRTI RESISTANCE

Mutation	Effects
TAMs	• Decrease susceptibility to all NRTIs • More TAMs = more NRTI cross-resistance
K65R	• Decreases susceptibility to TDF, ABC, 3TC, ddI, and ddC • Hypersusceptibility to AZT • Maintains susceptibility to d4T
L74V	• Decreases susceptibility to ddI, TDF, ABC, 3TC • Hypersusceptibility to AZT
M184V	• Confers high-level resistance to 3TC and lower level resistance to ABC • No major effect on ddI or TDF • Hypersusceptibility to ZDV
Multi-NRTI resistance	• Q151M complex: resistance to all NRTIs (but not TDF) • T69 insertion: Resistance to all NRTIs + TDF

NEVIRAPINE PATHWAYS



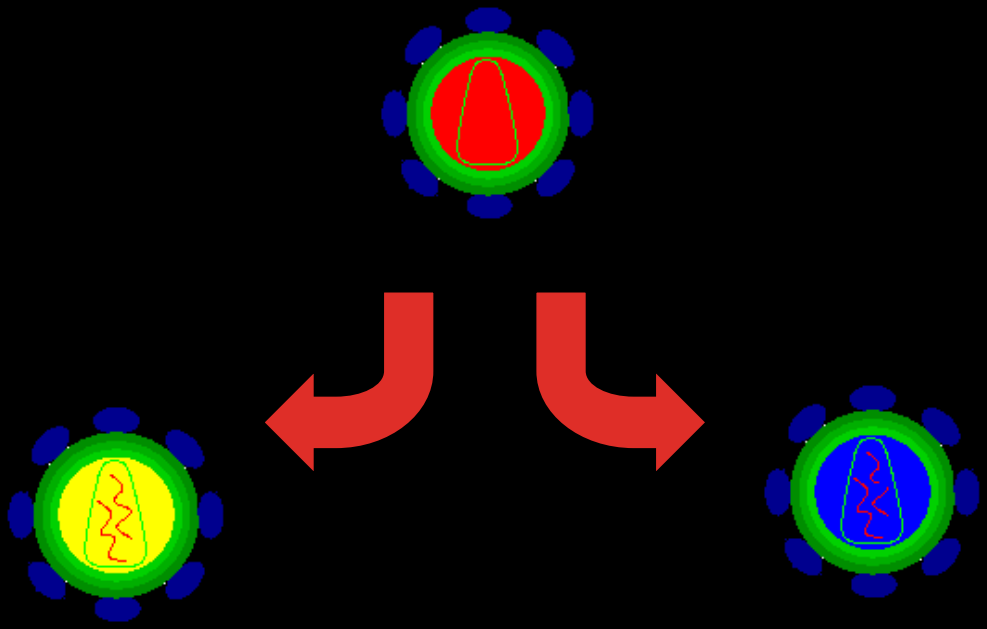
In the absence of AZT

In the presence of AZT

Y181C

K103N (almost always selected in EFV failures
regardless of nukes)

NELFINAVIR PATHWAYS



D30N (N88S

More common in SubType B virus and confers less cross resistance to subsequent PI's

L90M

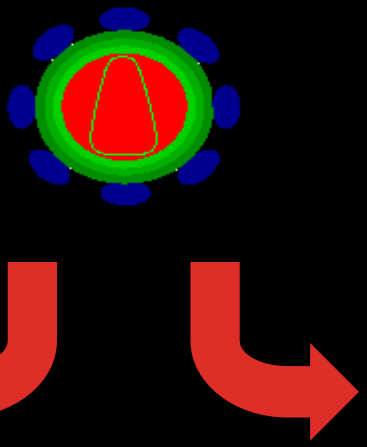
Less common and occurs more often with non-SubType B virus but confers more cross resistance to subsequent PI's

ATAZANAVIR PATHWAYS

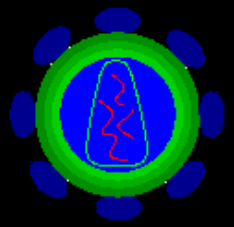
PI naïve or unboosted

I50L (N88S)

Confers hypersusceptibility to all other PI's?



Atazanavir boosted
Or PI experienced



Other key PR mutations at positions 48,82,84,90 and others in various combination

Confers cross-resistance to several other PI's

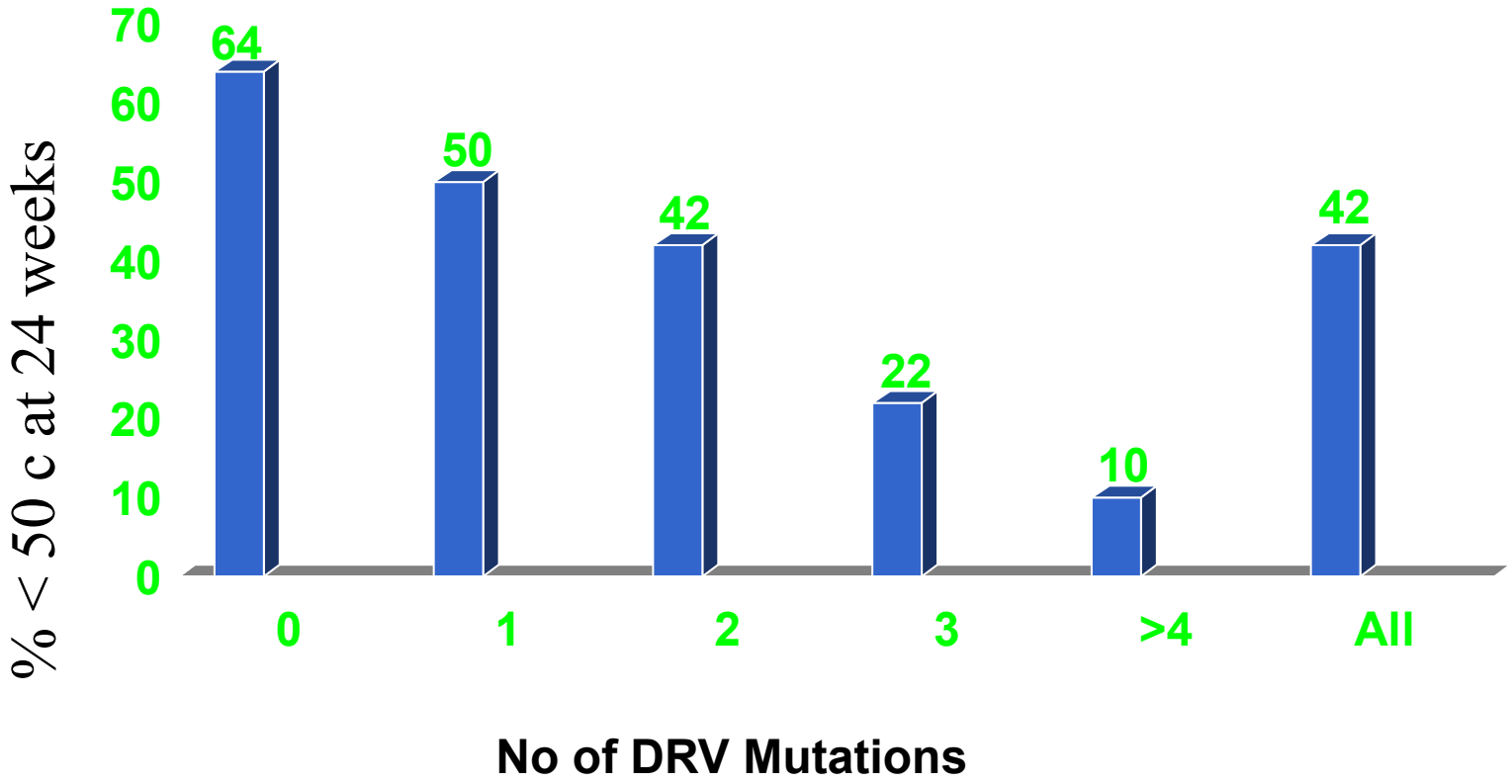
PRAMS SLIDE 82, 84, 90 (48)

- Protease Mutations most common in failures of first generation
- If alone, not as detrimental, but if combined, almost all first generation were lost
- Commonly popped up in first generation PR failures
- Sequencing was popular "TREAT for FAILURE vs TREAT for SUCCESS" -anticipate the next regimen.

WHAT ABOUT DARUNAVIR?

11 mutations associated with DRV resistance:

V11I, V32I, L33F, I47V, I50V, I54L or M, G73S, L76V, I84V, L89V

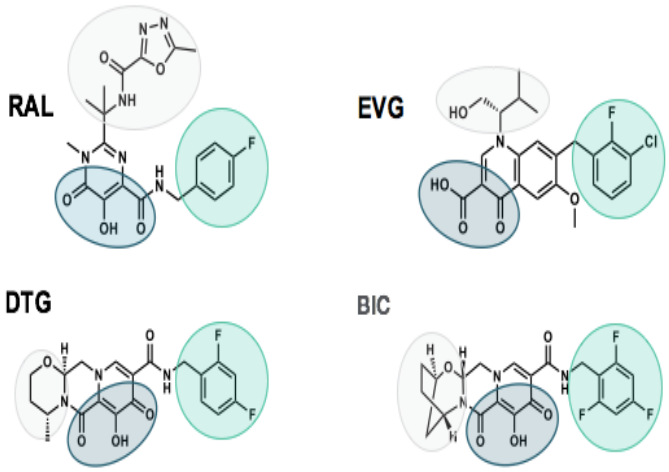


INTEGRASE INHIBITORS:

A LESSON IN CHEMICAL STRUCTURE

Mechanism of Action

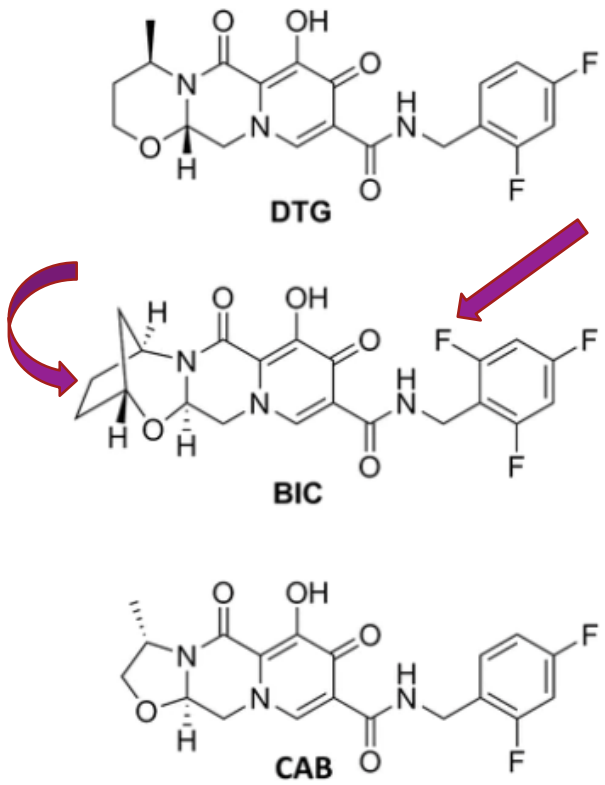
Metal-Chelating Core Halogenated Phenyl Ring Side Chain



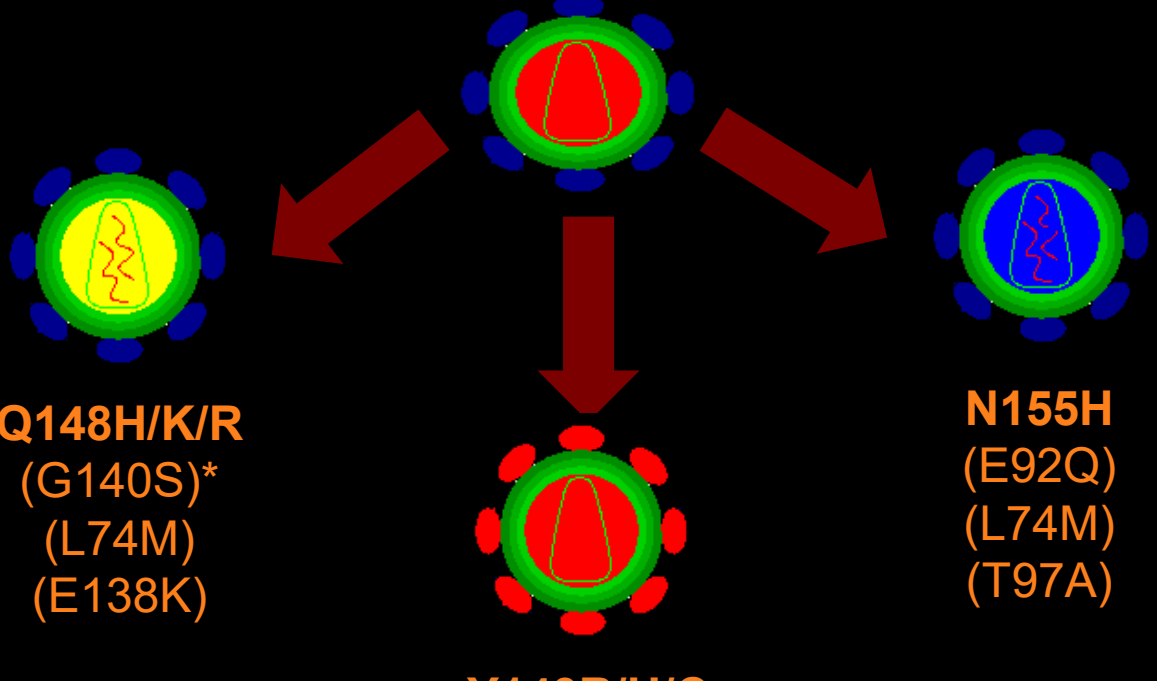
Metal-Chelating Core: Oxygen atoms chelate a pair of Mg^{2+} ions and bind the integrase catalytic active site

Halogenated Phenyl: Interacts with the integrase pocket that is normally occupied by the terminal 3' base of viral DNA

1. Lazerwith SE, et al. ASM 2016. Poster #414. 2. Gallant J, et al. ASM 2016. Poster #415. 3. Tsiang M, et al. ASM 2016. Poster #416. 4.Tsiang M, et al., AAC 2016;60:7086-7097.



RALTEGRAVIR PATHWAYS



Q148H/K/R
(G140S)*
(L74M)
(E138K)

Y143R/H/C
(least common)

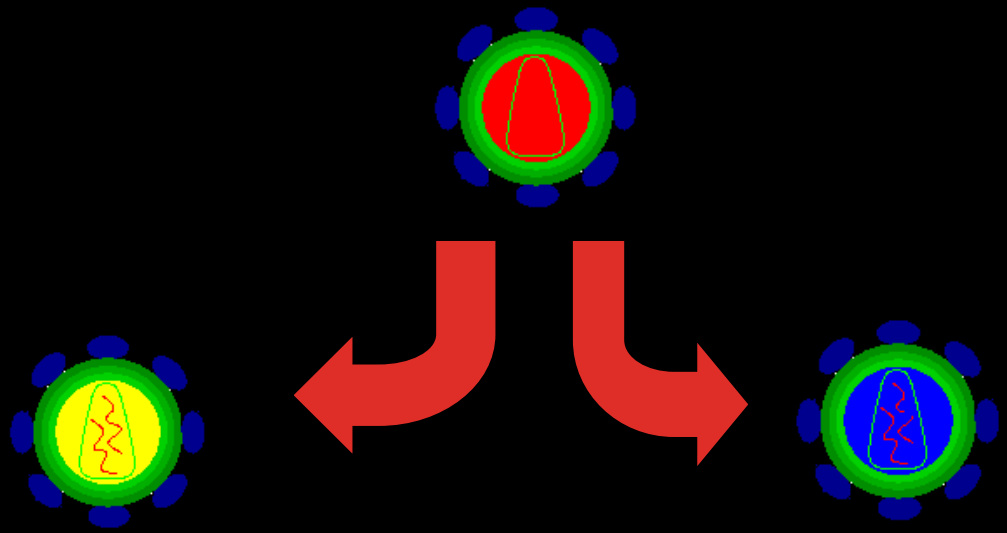
N155H
(E92Q)
(L74M)
(T97A)

***Elvitegravir RESISTANCE**

- **All of these confer cross resistance to EVG.**
- **92Q alone = 20 fold to EVG**

- **T66I/A/K signature for EVG.**

DOLUTEGRAVIR PATHWAYS



263K

118R

More common in SubType B virus and confers cross resistance to other II but only 2 fold

Becoming more common and occurs more often with non-SubType B virus AND confers high level resistance to DTG and other II's

RESISTANCE: SUBTYPE B VS. NON B

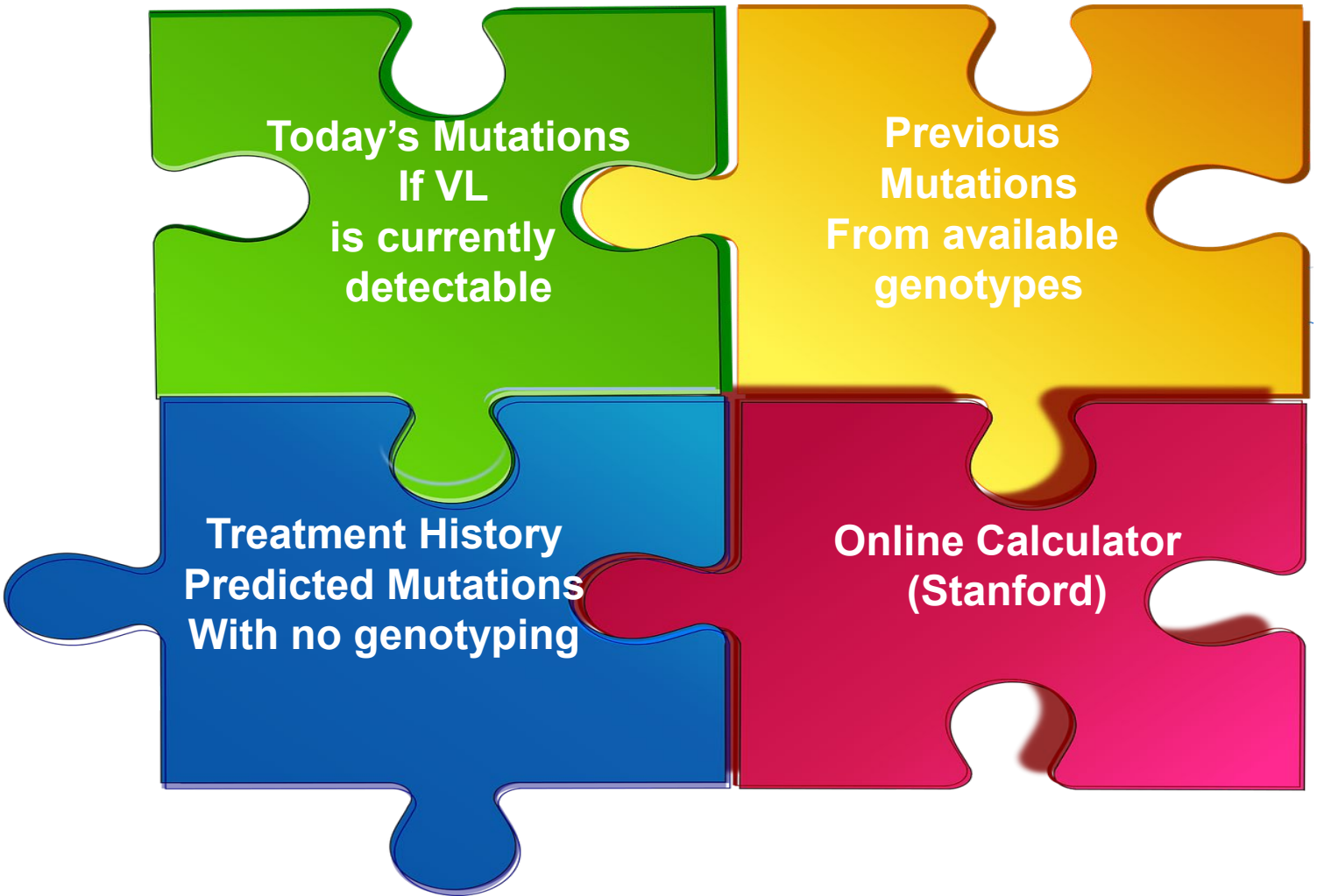
Class	Subtype B Pathway	Non-Subtype B Pathway
NRTI* *M184V/1 same for both	TAM 1: 41, 210W 215	TAM 2: 67,70,219 K65R more likely (C)
NNRTI	E138K twice as common	V106M more common (C)
PI	D30N	L90M
INSTI	263K	118R (C) (AG)

Microorganisms. 2023 Jan; 11(1): 221.
Published online 2023 Jan 15. doi: 10.3390/microorganisms11010221

HIV and Drug-Resistant Subtypes

Bianca Maria Nastri,[1] Pasquale Pagliano,[2,3] Carla Zannella,[1] Veronica Folliero,[1] Alfonso Masullo,[3] Luca Rinaldi,[4] Massimiliano Galdiero,[1] and Gianluigi Franci[2,5,*]

IF YOU CAN BUILD THIS PUZZLE YOU CAN BUILD THE BEST ART REGIMEN



WEB RESOURCES

- www.hivdb.stanford.edu -online mutation analysis
- www.hivresistanceweb.com - information
- www.aidsinfo.nih.gov/guidelines - guidelines
- www.iasusa.org – up to date guidelines and mutation charts

LINDA ROBINSON rxlinda@hotmail.com