
HIV Therapy and HIV Resistance

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HIV Resistance and Transmission

- Geographic Distribution based on ARV use
 - Data are based on population based sequencing
 - NRTI 8-10%
 - NNRTI 15%
 - PI 8-10%
 - Rates may be higher
 - >60% in NNRTI monotherapy studies
 - Fraction may be related to fitness of resistance mutations
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Drug Resistance as Therapy Advances

- Increasing ARV Coverage
 - Decreases prevalence
 - Prevents new infections
 - Requires substantial treatment coverage
 - Takes time
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Transmitted Drug Resistance

- Transmitted resistance increases
 - With time
 - With percent of infected patients on treatment
 - With endemic vs. epidemic spread
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Resistance: An Individual and a Global Concern

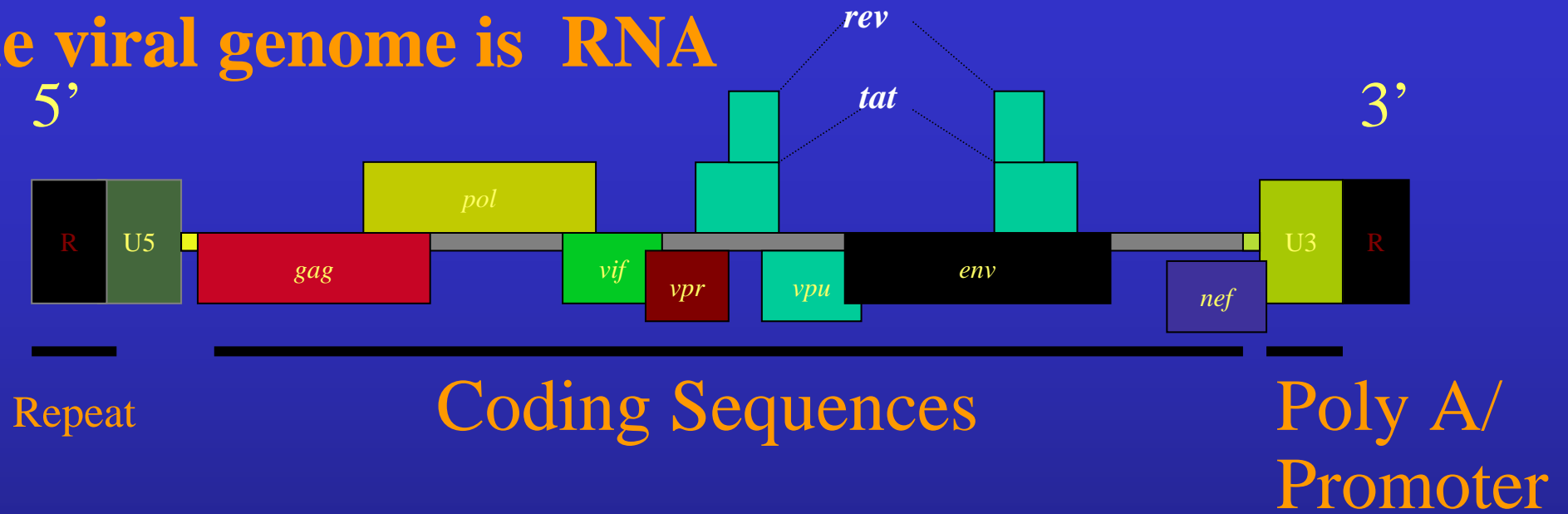
- Individual
 - Results in rebound viremia and death if untreated
 - Limits choices for subsequent therapy
 - Regimens become more complex
 - Global
 - Multiple regimens are more expensive to treat
 - Resistance may be spread at the time of transmission
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Resistance: An Individual and a Global Concern

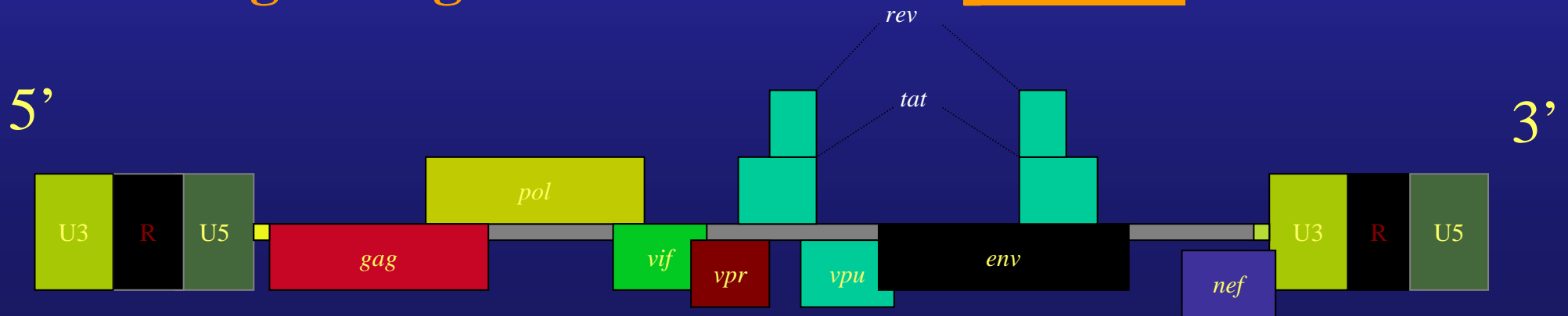
- Individual Concern
 - Estimates 20- 40% patients on therapy may develop resistance
 - Higher rates with older regimens
 - Global Concern
 - Transmitted Resistance
 - 15% for NNRTI class
 - 5-10% for NRTI
 - 5-10% for PI
 - Reverses gains realized by drug development
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Retroviruses Conventions

The viral genome is **RNA**



The integrated genome is called the provirus



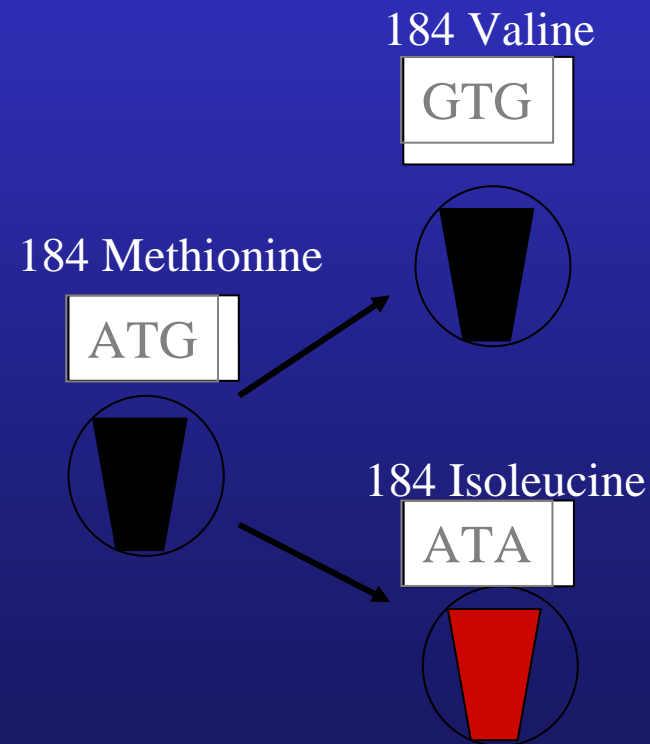
Retroviruses Systematic Anatomy

Glossary

- *gag*: **g**roup **a**ntigen
 - *pol*: **p**olymerase
 - *env*: **e**nvelope
 - *tat*: **T**rans**a**ctivator
 - *rev*: **R**egulator of **E**xpression of **V**irion **p**roteins
 - U3: unique sequence in 3' region
 - U5: Unique sequence in 5' region
 - R: Repeat sequence
 - PBS Primer binding site for initiation of RT
 - Ppt: polypurine tract primer for RT
 - TAR: Tat activating sequence
 - RRE: Rev responsive element
 - Provirus: copy of retrovirus that is integrated into host genome
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Rapid and Error-Prone HIV Replication is a Pathogenic Determinant

- Each round of HIV replication generates numerous mutants.
- The ability of the mutants to replicate (viral “fitness”) may vary greatly.
- Some are tolerated at a low frequency
- A diverse population permits dynamic response to selective pressure



THE MUTANTS ARE LIKELY TO EXIST PRIOR TO THE THERAPY

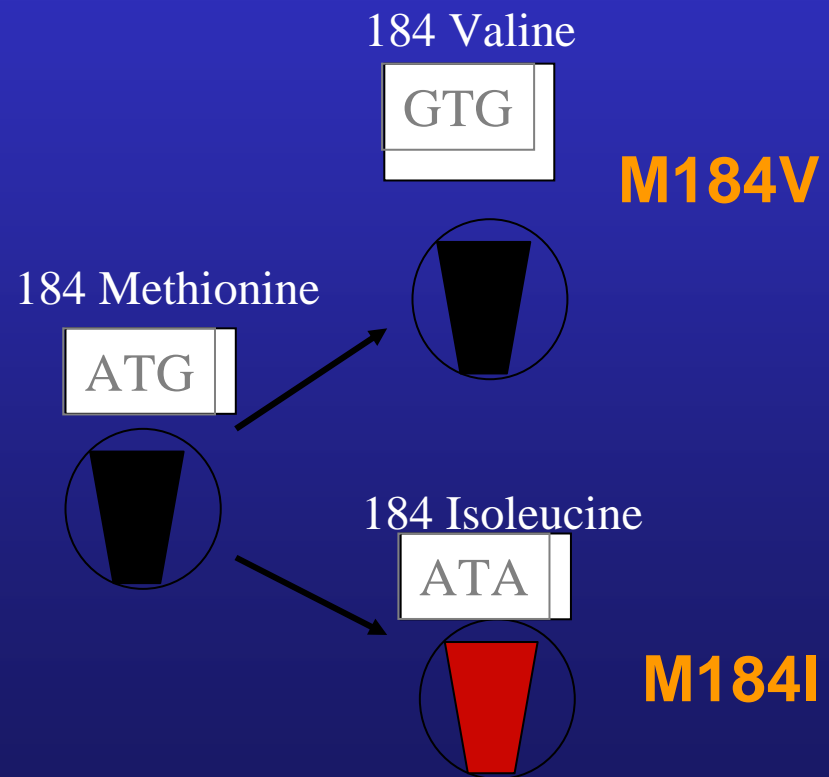
Presence of one mutant in RT region is relatively likely

- two in same genome unlikely
- three is highly statistically unfavorable
 - Individual mutations may be assembled through recombination

Drug therapy is a selective pressure that permits resistant viruses to emerge

Conventions Labeling The Mutant

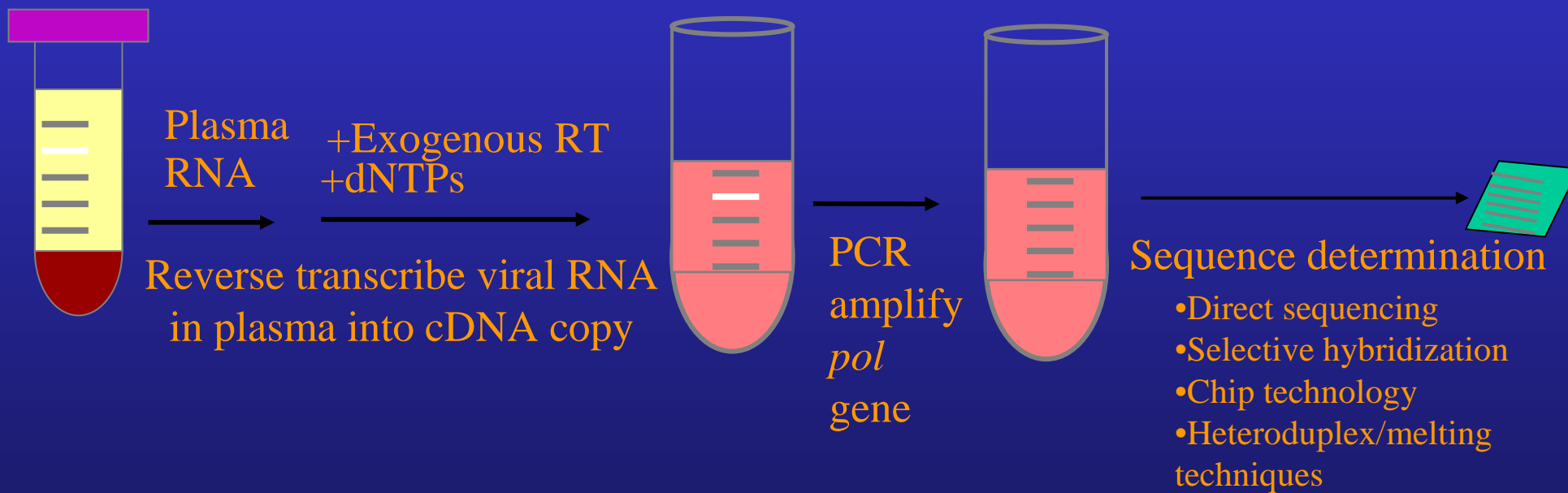
- First letter: M = the single letter amino acid code of the wild type virus
- Number= Amino acid position in the protein (RT, protease, envelope)
- Second letter: V the single letter amino acid code of the mutant virus



Methods to Detect Resistance

- Genotyping
 - Phenotyping
 - Virtual Phenotyping
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HIV Genotyping



HIV Genotyping

- Advantages
 - Relatively rapid
 - Technically facile
 - Large database of information for most drugs
 - Disadvantages
 - Mutant must be >20-25% to be represented
 - Identifies resistance; susceptibility is inferred
 - Certain mutations seen in vitro may not correlate well in vivo (ddl, d4T)
 - May be complex
 - New drugs have little data
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Interpretation of Genotypes

- 'Expert Opinion'
 - Not 100% agreement among experts
 - Difficult to convene experts and publish new guidelines in timely manner
 - Rules-based Algorithms
 - Agreement needed on algorithm
 - Updates needed frequently
 - *None are designed to be clinical management tools – only provide guidance*
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HIV Phenotyping

- Advantages

- Direct measure of susceptibility using clinically obtained HIV enzymes
- Assay drugs with less clinical knowledge of genotyping

- Disadvantages

- Adaptation to tissue culture is contrived
- No standards for cutoff values
- Sensitivity uncertain but likely low 20% rule applies
- Weeks until results available

- Cutoffs are:

- Clear from *in vitro* data alone
 - 3TC: 50-100X resistance
 - NNRTI: >50X resistance
 - Derived clinical and *in vitro*
 - ABC ($\geq 4X$)
 - LPV/RTV ($\geq 10X$)
 - Subtle
 - D4T (~1.8 X)
 - ddI (~1.8 X)
-

*VirtualPhenotype*TM Cut-Offs

- *VirtualPhenotype*TM cut-offs are very similar to those for the Antivirogram[®]
 - Similar genotype-phenotype algorithms are available in Web based format
 - geno2pheno
-

Common Mutations (RTIs)

- M184V: 3TC (ddC) – Important since this single mutation renders HIV completely resistant to 3TC
 - K103N: Important since this single mutation renders HIV completely resistant to NNRTIs (EFV, NVP)
 - M41L, D67N, K70R, L210W, T215Y:TAMS – Generally, other NRTIs require more than a single mutation in the RT to be completely ineffective against HIV
 - Q151M, F77L, F116Y : Multi-NRTI resistant
(Tenofovir may have some activity against Q151M)
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Other Common Mutations (PIs)

- Whereas the NNRTI class is completely ineffective against HIV with the K103N mutation in the RT, and 3TC is completely ineffective against HIV with the M184V mutation, other NRTIs require more than a single gene mutation to be rendered ineffective
 - The PI class of antiretrovirals is even more resistant to mutations; they often require 5 or more mutations in the protease gene for HIV to be completely resistant to PIs; consequently, we often see complete resistance to NNRTIs, but only relative resistance to the PIs.
 - An exception to this is the D30N mutation which is specific for the PI Nelfinavir.
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Inhibitors of HIV-1 Reverse Transcriptase

- N(t)RTIs

- Analogues of natural nucleotides or nucleosides
 - AZT (T), d4T (T) 3TC (C), DDI (A), ddC (C), Abacavir (G),
 - Nucleotide reverse transcriptase inhibitors
 - Tenofovir (A), Adefovir (A)
- incorporated into the growing strand
- Inhibit further polymerization by preventing addition of additional nucleotides “Chain terminators”

- NNRTI

- Noncompetitive inhibitors
 - Nevirapine
 - Efavirenz
 - Delavirdine
 - TMC-125



Are There Any Good Mutants?

- A change that may confer resistance to one drug but offer sensitivity to another?
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Are There Any Good Mutants?

3TC Resistance (M184V)

- Viruses with TAMS (M41L, D67N, K70R, T215Y) have some residual activity to AZT, D4T, and tenofovir)
 - Residual activity is GREATER if the additional mutation M184V is present.
 - Clear superior benefit of AZT+3TC over AZT monotherapy in early chemotherapy
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Are There Any Good Mutants?

TDF Resistance (K65R)

- Resistant to TDF but more sensitive to AZT

TAM 215Y/F

- Resistant to AZT, D4T, ddI
 - More sensitive to TDF
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Are There Any Good Mutants?

NNRTI Hypersusceptibility

- Accumulation of NRTI resistance mutations makes viruses more (~2 X) susceptible to NNRTI
 - They DO NOT reverse NNRTI Resistance mutations
 - Clinical benefit has been reported
 - Prompts suggestion to start with a PI-based regimen and salvage with NNRTI-based regimen if NRTI resistance accumulates
 - Benefit may be outweighed by additional considerations
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Resistance and T-20

- Selected within weeks of monotherapy
 - Associated with specific mutations 36, 42, 43, 44
 - Resistance 15-400 X
 - Suggestion that continued therapy during viremia may result in lower viremia
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- But NO ONE with highly resistant viruses achieved viral RNA levels <50 copies/ml
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NRTI Hypersusceptibility

- Viruses that are more susceptible than WT to NRTIs
 - Antagonism between K65R and TAMs pathways
 - K65R is more sensitive to AZT than WT
 - T215Y/F is more sensitive to Tenofovir than WT
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New Antiviral Targets

- Integrase
 - Coreceptor
 - RT
 - Connection domain
 - RNase H
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Integrase

- Critical event in HIV replication
 - Inhibitors are potent
 - 2-log reduction
 - Effective in setting of previous drug resistance
 - STILL NEED at least another agent for salvage therapy
 - Approx. 50% responses (viral RNA <500 copies/ml) in drug resistant patients in the absence of additional effective agents
 - The genetic barrier remains unclear
 - Not a PI
 - Not an NNRTI
 - In a class by itself
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Coreceptor inhibitor

- Coreceptor switch
 - CCR5 coreceptor “switch” to CXCR4 in late stage disease
 - Switch thought to portend
 - Population based sequencing data
 - Occurs in approx. 50% progression
 - The other 50% progress with CCR5 preferring virus
 - “Switch” evident in early trials (population based)
 - Both coreceptors likely present at all times
 - Impact remains unclear
 - So maybe a switch at higher CD4 cell counts is a good thing
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DHHS Recommendations for HIV Resistance Testing

- Recommended
 - Virologic failure on treatment
 - Suboptimal suppression after initiation
 - Primary HIV infection
 - Chronic HIV infection prior to starting therapy
 - In care but not yet requiring therapy (Dec 2007)
 - All pregnant women prior to initiation of therapy and those entering pregnancy with detectable HIV RNA levels
 - Not generally recommended
 - After discontinuation of drugs
 - For viral load levels <1000 copies/ml
 - DHHS Guidelines for Therapy
 - www.hivactis.org
-

Web-Based Resources for Drug Resistance

- Resistance Databases

- Stanford Database

- <http://hivdb.stanford.edu/>

- Los Alamos HIV Drug Resistance database

- http://resdb.lanl.gov/Resist_DB/default.htm

- Genotype to phenotype

- www.geno2pheno.org/cgi-bin/geno2pheno.pl

- PIRSpred

- <http://protinfo.compbio.washington.edu/pirspred/>

- HIV Resistance Web

- www.hivresistanceweb.com/index.shtml

- HIV Drug Resistance

- <http://www.retrovirus.info/>

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