

# Drug Resistance Reports

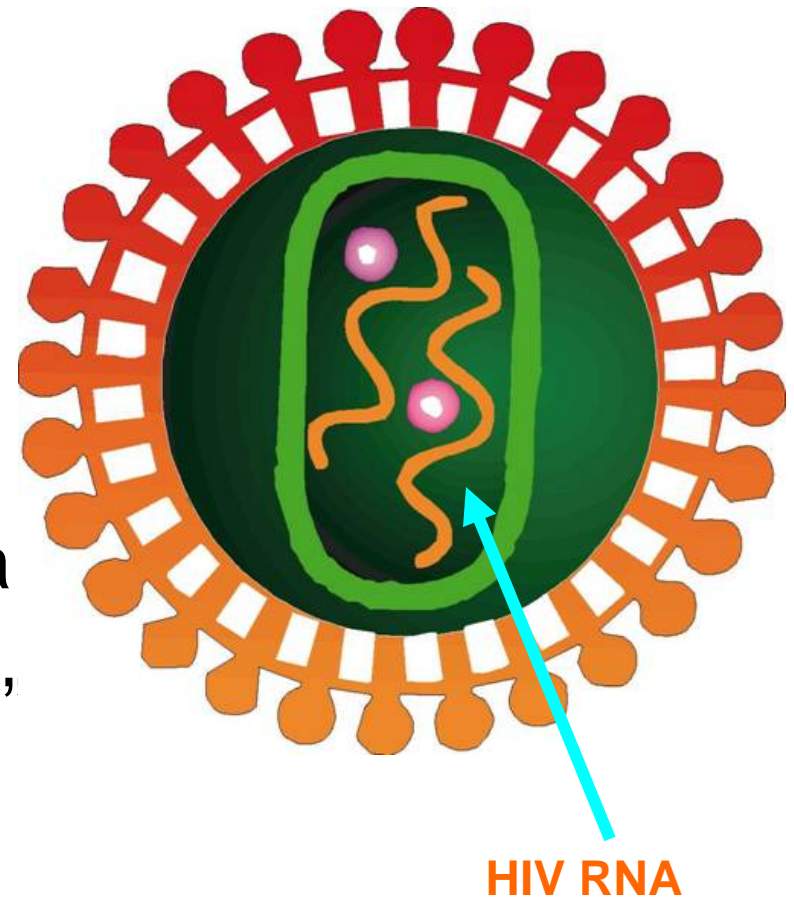
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MTN-009 Training  
Durban, South Africa  
May 7, 2010



# What is resistance testing?

- HIV-1 has genetic material called RNA
- Using a laboratory test, we can determine the DNA sequence of HIV's genetic material.
- Standard resistance testing compares the sequence of virus from a patient to a known "consensus" or "wildtype" HIV sequence



# Drug Resistance Testing

- Laboratory Testing for HIV Drug Resistance will be done at Network Lab
- Resistance tests include:
  - **Standard Resistance Test**
  - **Sensitive Resistance Test**



# What is the difference?

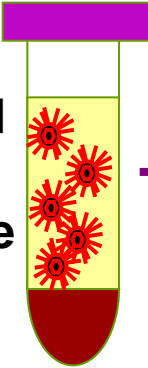
Method	Type	Description
<b>VIROSEQ (Standard)</b>	CLINICAL (USA FDA- approved)	Population genotype – major mutations
<b>ASPCR (Sensitive)</b>	RESEARCH ONLY	% of a specific mutant

# How will we use the data?

Method	What we learn
<b>VIROSEQ (Standard)</b>	The resistance mutations seen can help a physician decide what therapy to put a patient on
<b>ASPCR (Sensitive)</b>	Gives an idea if patient has “undetected” resistance, and to what extent

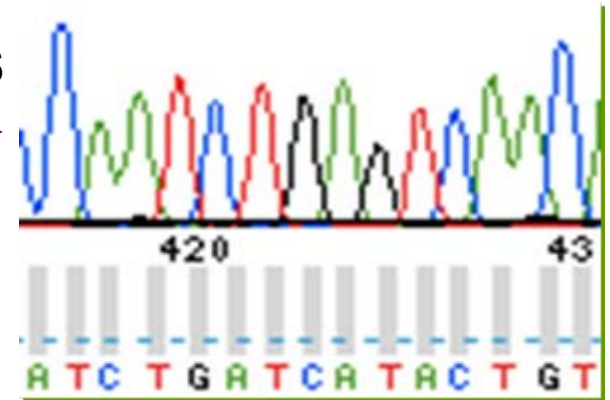
# Standard Resistance Test (ViroSeq)

Plasma shipped to NL from site



Lab Procedures for Standard Resistance Test

RESULTS



STANDARD SEQUENCE

Results sent to SCHARP on CRF

Detects the "majority" or "population" variant

Misses bases present at <25%

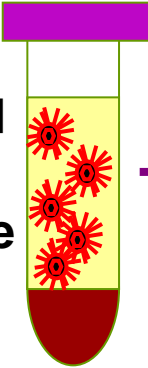
**ViroSeq™ HIV-1 Antiretroviral Drug Resistance Report**

Patient ID Patient Name Last Patient Name First MI Accession Number Patient Gender Patient Birthdate & Age Report Generated by Report Date & Time Ordering Physician Institution Date Drawn Assay Operator Field1 Field2	Testing Laboratory Lab Director Department ID Mailstop Street Address1 Street Address2 City State/Province Postal Code Country Telephone/Fax E-mail Web Site	
Drug Class	Drug	Evidence of Resistance
NRTI	EPVIR® (zidovudine, ZTC)	Resistance***
	EMTRIVA® (emtricitabine, FTC)	Resistance***
	RETROVIR® (zidovudine, AZT)	Resistance***
	VIDEX® (didanosine, ddi)	Resistance***
NNRTI	ZENITH® (stavudine, d4T)	Resistance***
	ZIAGEN® (abacavir, ABC)	Resistance***
	VIREAD® (tenofovir, TDF)	Resistance***
	RESCRIPTOR® (delavirdine, DLV)	None
PI*	SUSTIVA® (efavirenz, EFV)	None
	VIRAMUNE® (nevirapine, NVP)	None
	AGENERASE® (amprenavir, APV)	Resistance***
	LEKIVA® (ritonavir, R05)	Resistance***
	CRIVAN® (indinavir, IDV)	Resistance***
	FORTOVA® / INVIRASE® (saquinavir, SQV)	Resistance***
	KALETRA® (lopinavir + ritonavir, LPV)	Resistance***
	NORVIR® (nelfinavir, NFV)	Resistance***
VIRACEPT® (zalcitabine, ZDV)	Resistance***	
REYATAZ® (atazanavir, ATV)	Resistance***	
APTIVUS® (tipranavir, TPV)	Resistance***	
Drug Class	Drug Resistance Mutations Identified	
NRTI	M41L, A62V, T69A, T69ns, V118I, M184V, T215Y	

Resistance Report sent to site

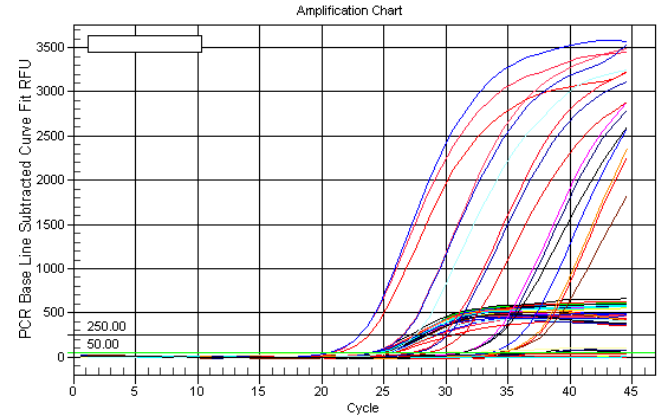
# Sensitive Resistance Test (ASPCR)

Plasma shipped to NL from site



Lab Procedures for Sensitive Resistance Test

RESULTS



Calculate proportion of wild type and mutant from Real Time PCR results

A screenshot of a CRF form titled "Network Lab Sensitive Genotyping Test Results and Infection Type (NLS-2)". The form includes fields for "Participant ID" (Site number, Participant number, CTR) and "Network Lab Sensitive Genotyping Test Results and Infection Type". It contains two sections for resistance testing: "3a. FTC Resistance (Codon 154)" with sub-sections 3a1 (M), 3a2 (I), and 3a3 (V); and "3b. Tenofvir Resistance (Codon 65)" with sub-sections 3b1 (K) and 3b2 (R). Each sub-section has a percentage field. The form is marked "not done" for each section. A purple arrow points from the text "Detects mutations present at 0.1% or higher" to this form.

Detects mutations present at 0.1% or higher

Test one mutation at a time

Results cannot be used for clinical management

Results sent to SCHARP by CRF  
Results **NOT** sent to site.

# Standard Resistance Report - TOP



## ViroSeq™ HIV-1 Antiretroviral Drug Resistance Report

Patient ID	208-000xxxxx	Testing Laboratory	MTN Virology CORE
Patient Name Last	----	Lab Director	Urvi Parikh PhD Assoc Dir
Patient Name First MI	---- -	Department ID	
Accession Number	----	Mailstop	
Patient Gender	Female	Street Address1	S804 Scaife Hall
Patient Birthdate & Age		Street Address2	3550 Terrace St
Report Generated By	admin	City	Pittsburgh
Report Date & Time	15 Apr 2010, 03:12:23 PM, EDT	State/Province	PA
Ordering Physician	----	Postal Code	15216
Institution	Durban	Country	USA
Date Drawn		Telephone/Fax	Ph: 412-648-3103 Fax: 412-648-8521
Assay Operator	Kelley Gordon	E-mail	ump3@pitt.edu
Field1	MTN-009	Web Site	www.mtnstopshiv.org
Field2	----		



# No Resistance

Drug Class	Drug	Evidence of Resistance
NRTI	EPIVIR® (lamivudine, 3TC)	None
	EMTRIVA® (emtricitabine, FTC)	None
	RETROVIR® (zidovudine, AZT)	None
	VIDEX® (didanosine, ddl)	None
	ZERIT® (stavudine, d4T)	None
	ZIAGEN® (abacavir, ABC)	None
	VIREAD® (tenofovir, TDF)	None
NNRTI	RESCRIPTOR® (delavirdine, DLV)	None
	SUSTIVA® (efavirenz, EFV)	None
	VIRAMUNE® (nevirapine, NVP)	None
	INTELENCE™ (etravirine, ETR)	None
PI <sup>+</sup>	AGENERASE® (amprenavir, APV)	None
	LEXIVA® (fosamprenavir, FOS)	None
	CRIVAN® (indinavir, IDV)	None
	FORTOVASE® / INVIRASE® (saquinavir, SQV)	None
	KALETRA® (lopinavir + ritonavir, LPV)	None
	PREZISTA® (darunavir, DRV)	None
	VIRACEPT® (nelfinavir, NFV)	None
	REYATAZ® (atazanavir, ATV)	None
	APTIVUS® (tipranavir, TPV)	None

Drug Class	Drug Resistance Mutations Identified
NRTI	
NNRTI	
PI	

# Resistance

Drug Class	Drug	Evidence of Resistance
NRTI	EPIVIR® (lamivudine, 3TC)	None
	EMTRIVA® (emtricitabine, FTC)	None
	RETROVIR® (zidovudine, AZT)	None
	VIDEX® (didanosine, ddl)	None
	ZERIT® (stavudine, d4T)	None
	ZIAGEN® (abacavir, ABC)	None
	VIREAD® (tenofovir, TDF)	None
NNRTI	RESCRIPTOR® (delavirdine, DLV)	Resistance
	SUSTIVA® (efavirenz, EFV)	Resistance
	VIRAMUNE® (nevirapine, NVP)	Resistance
	INTELENCE™ (etravirine, ETR)	None
PI <sup>+</sup>	AGENERASE® (amprenavir, APV)	None
	LEXIVA® (fosamprenavir, FOS)	None
	CRIVAN® (indinavir, IDV)	None
	FORTOVASE® / INVIRASE® (saquinavir, SQV)	None
	KALETRA® (lopinavir + ritonavir, LPV)	None
	PREZISTA® (darunavir, DRV)	None
	VIRACEPT® (nelfinavir, NFV)	None
	REYATAZ® (atazanavir, ATV)	None
	APTIVUS® (tipranavir, TPV)	None
Drug Class	Drug Resistance Mutations Identified	
NRTI		
NNRTI	K103N	
PI		

# Possible Resistance

Drug Class	Drug	Evidence of Resistance
NRTI	<i>EPIVIR®</i> ( <i>lamivudine, 3TC</i> )	<i>Possible Resistance*</i>
	<i>EMTRIVA®</i> ( <i>emtricitabine, FTC</i> )	<i>Possible Resistance*</i>
	<i>RETROVIR®</i> (zidovudine, AZT)	Resistance*
	<i>VIDEX®</i> (didanosine, ddi)	Resistance*
	<i>ZERIT®</i> (stavudine, d4T)	Resistance*
	<i>ZIAGEN®</i> (abacavir, ABC)	Resistance*
	<i>VIREAD®</i> (tenofovir, TDF)	Resistance*
NNRTI	<i>RESCRIPTOR®</i> (delavirdine, DLV)	Resistance*
	<i>SUSTIVA®</i> (efavirenz, EFV)	Resistance*
	<i>VIRAMUNE®</i> (nevirapine, NVP)	Resistance*
	<b>INTELENCE™</b> ( <b>etravirine, ETR</b> )	<b>None</b>
PI <sup>+</sup>	<i>AGENERASE®</i> (amprenavir, APV)	Resistance***
	<i>LEXIVA®</i> (fosamprenavir, FOS)	Resistance***
	<i>CRIVAN®</i> (indinavir, IDV)	Resistance***
	<i>FORTOVASE® / INVIRASE®</i> (saquinavir, SQV)	Resistance***
	<i>KALETRA®</i> (lopinavir + ritonavir, LPV)	Resistance***
	<b>PREZISTA®</b> ( <b>darunavir, DRV</b> )	<b>None</b>
	<i>VIRACEPT®</i> (nelfinavir, NFV)	Resistance***
	<i>REYATAZ®</i> (atazanavir, ATV)	Resistance***
<i>APTIVUS®</i> (tipranavir, TPV)	Resistance***	
Drug Class	Drug Resistance Mutations Identified	
NRTI	M41L, E44D, A62V, D67N, L74V, L210W, T215Y	
NNRTI	L100I, K103N	
PI	L10I, L23I, L33F, M46L, I54V, A71I, A71T, V82A, L90M	

# Possible Resistance

Examples seen in MTN-015 participant report.

- V179D
- K101Q
- K103R
- M46I

**Not known to cause resistance**

**Caution with algorithms**

	PREZISTA®	(darunavir, DRV)	None
	VIRACEPT®	(nelfinavir, NFV)	Possible Resistance
	REYATAZ®	(atazanavir, ATV)	None
	APTIVUS®	(tipranavir, TPV)	None
Drug Class	Drug Resistance Mutations Identified		

# Other Mutations

## *From Resistance Report*

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**Additional Mutations:** The following amino acids differing from the reference sequence (HXB-2, accession number K03455) at the indicated codon positions were identified and may be useful as a baseline determination of virus genotype.

### Protease:

Q2L, Q2R, V3I, T12S, I15V, L19I, E35D, M36I, S37N, R41K, D60E, L63P, C67Y, H69K, V82I, L89M, I93L

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### Reverse Transcriptase:

V35T, T39E, S48T, V60I, I135T, K173T, T200A, Q207K, R211A, L214F, V245Q, E248D, P272A, R277K, E291D, V292I, I293V, V317A, S322T, I329L, Q334E

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- All differences from reference HXB2 Subtype B sequence appear here
- Most are polymorphisms specific to Subtype C

# ARV Resistance in MTN-009

- Only HIV-positive MTN-009 participants will get a drug resistance test
- The results of an HIV resistance test may help a doctor decide which ARVs to use for HIV therapy
- Disseminating these results will be the last MTN-009 study visit.
  - After this visit, participants have completed the MTN-009 study.
  - Participants are ineligible to screen for or participate in an HIV prevention trial after exiting the study.