PhenoSense™ HIV :
Rapid phenotypic drug susceptibility assay

Nicholas Hellmann, M.D.
ViroLogic, Inc.

ViroLogic

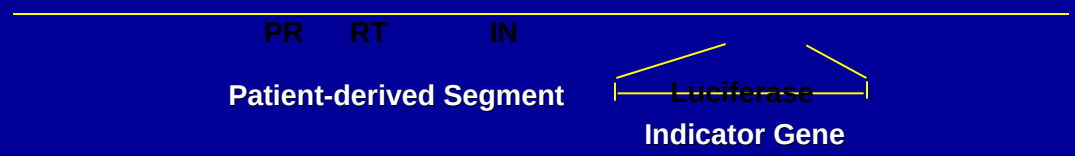
PhenoSense HIV:
Phenotypic drug susceptibility assay

- PhenoSense HIV is a novel, rapid, recombinant virus, phenotypic drug susceptibility assay for HIV-1.
- The assay is intended for use in the clinical management of HIV-infected patients by clinicians making antiretroviral treatment decisions.
- The assay measures the drug susceptibility of HIV-1 from plasma or serum samples containing $\geq$ 500 HIV RNA copies per mL.
- The assay simultaneously tests the susceptibility of HIV against all approved antiretroviral drugs.
- The assay is performed in 8-10 days with a turn-around time of 14 days or less from sample receipt to report of results

ViroLogic

ViroLogic PhenoSense™ HIV Assay

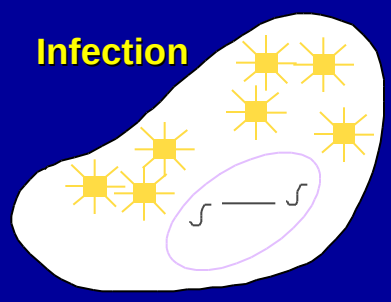
Resistance Test Vector DNA



Resistance Test Vector DNA + A-MLV *env* DNA

Transfection

Infection



PR Inhibition

Phenosense HIV Validation Experiments

- More than 2000 PhenoSense HIV assays were performed in a battery of experiments to validate assay performance characteristics
- The experiments utilized patient plasma or serum samples, virus clones, or site-directed mutant viruses
- All PhenoSense HIV assays were performed in the ViroLogic Clinical Reference Laboratory (South San Francisco, CA, USA)
- The validation experiments evaluated the accuracy, precision, specificity, sensitivity, and linearity of the assay.

ViroLogic

PhenoSense HIV: Validation results

- PhenoSense™ HIV is a sensitive, accurate, and reproducible phenotypic drug susceptibility assay for HIV-1
  - performed on plasma samples with viral loads $\geq$ 500 copies/mL
  - accurately tests all FDA-approved antiretroviral drugs
  - results vary less than 2.5 fold with repeated testing by multiple operators, across multiple assay runs, and with multiple lots of reagents
  - results are not significantly affected by common interfering substances or variations in virus concentrations in plasma.
  - minor populations of drug resistant virus can be detected at concentrations as low as 10%
  - can be used to test non-B clade HIV-1 strains

ViroLogic

Potential Clinical Utility of PhenoSense HIV

- Treatment decisions after failure of therapy
- Treatment decisions at time of treatment initiation
- Monitoring for onset of viral resistance
- Determining optimal treatments in a population

ViroLogic

Correlation of Baseline Phenotypic Drug Susceptibility with 16 Week Virologic Response in a Pilot Combination Therapy Study in HIV-infected Patients Who Failed Indinavir Therapy

S.G. Deeks[1], N. Parkin[2], C.J. Petropoulos[2], R.M. Grant[3], P.A. Volberding[1], J. Whitcomb[2], H. Tian[2], T. Wrin[2], K. Limoli[2], B. Drews[3], M. Warmerdam[3], N.S. Hellmann[2]

1 UCSF AIDS Program, San Francisco, CA, USA;
2 ViroLogic, Inc., South San Francisco, CA, USA;
3 Gladstone Institute of Virology and Immunology, UCSF, San Francisco, CA, USA

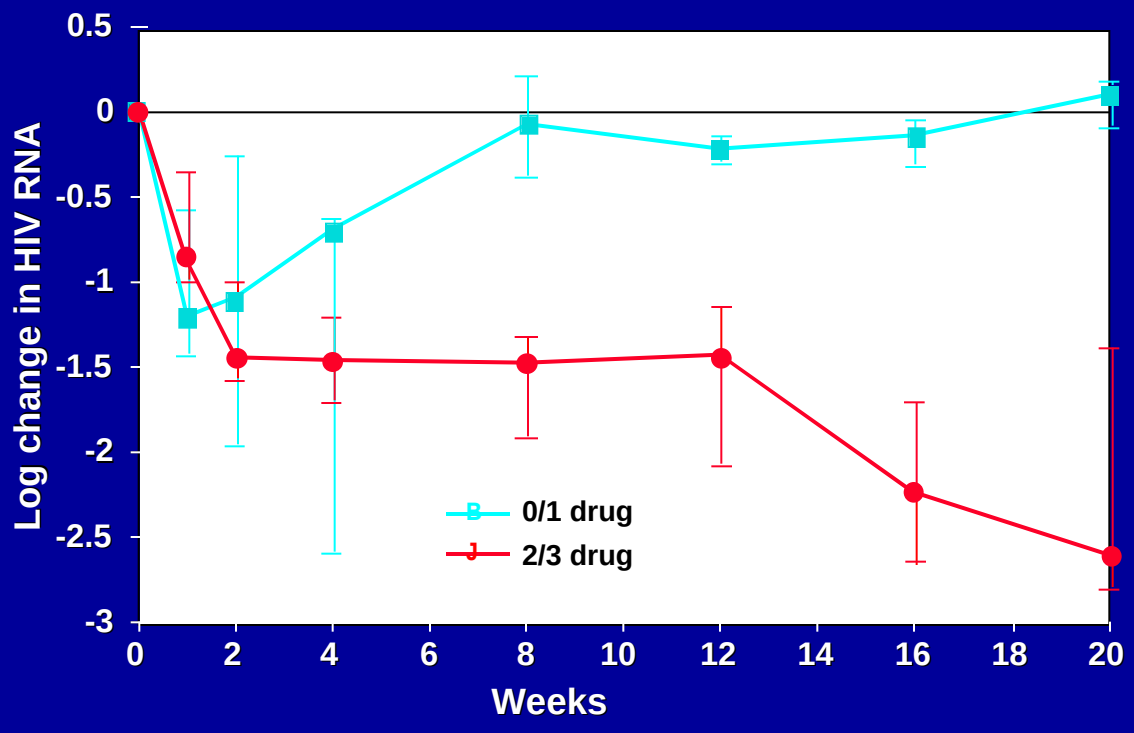
ViroLogic

Study Design

- Prospective, open-label pilot salvage therapy trial
- Entry criteria:
  - Failed > 24 weeks prior IDV combination therapy
  - Plasma HIV RNA > 2500 copies/mL
  - No prior therapy with SQV, NFV, ABC, NNRTI
- Treatment regimens:
  - SQVsgc+NFV+ABC+NRTI (n=10)
  - SQVsgc+NFV+ABC+NVP (n=10)
    (Doses: NFV 1250 mg BID, SQVsgc 1200 mg BID, ABC 300 mg BID, NVP 200mg BID)
- Sample size: 20 patients
- Outcome: change in plasma HIV RNA

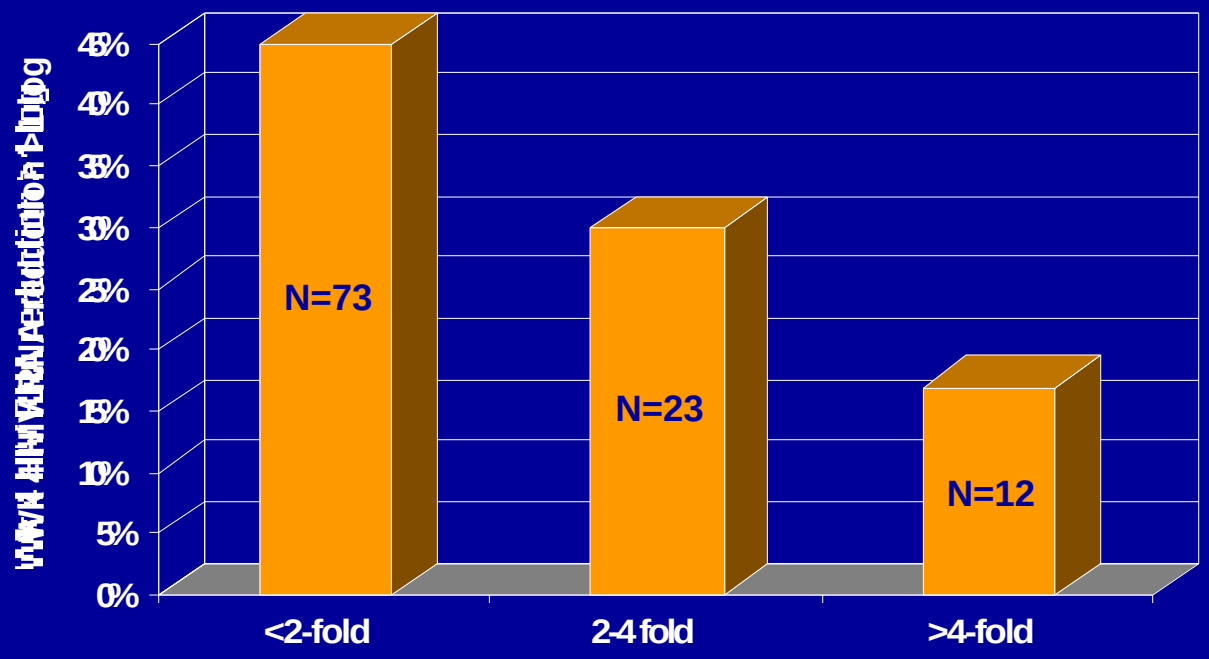
ViroLogic

Baseline Virus Sensitive to 0 or 1 vs. 2 or 3 Drugs
Median (±25%) Change in Plasma HIV RNA



ViroLogic

AmFAR 3TC Trial: Correlation between 3TC fold-change and virologic response



Skowron, et al : 3rd Intl Workshop on HIV Drug Resistance, June 1999

ViroLogic

Potential Clinical Utility of PhenoSense HIV

- Treatment decisions after failure of therapy
- **Treatment decisions at time of treatment initiation**
- Monitoring for onset of viral resistance
- Determining optimal treatments in a population

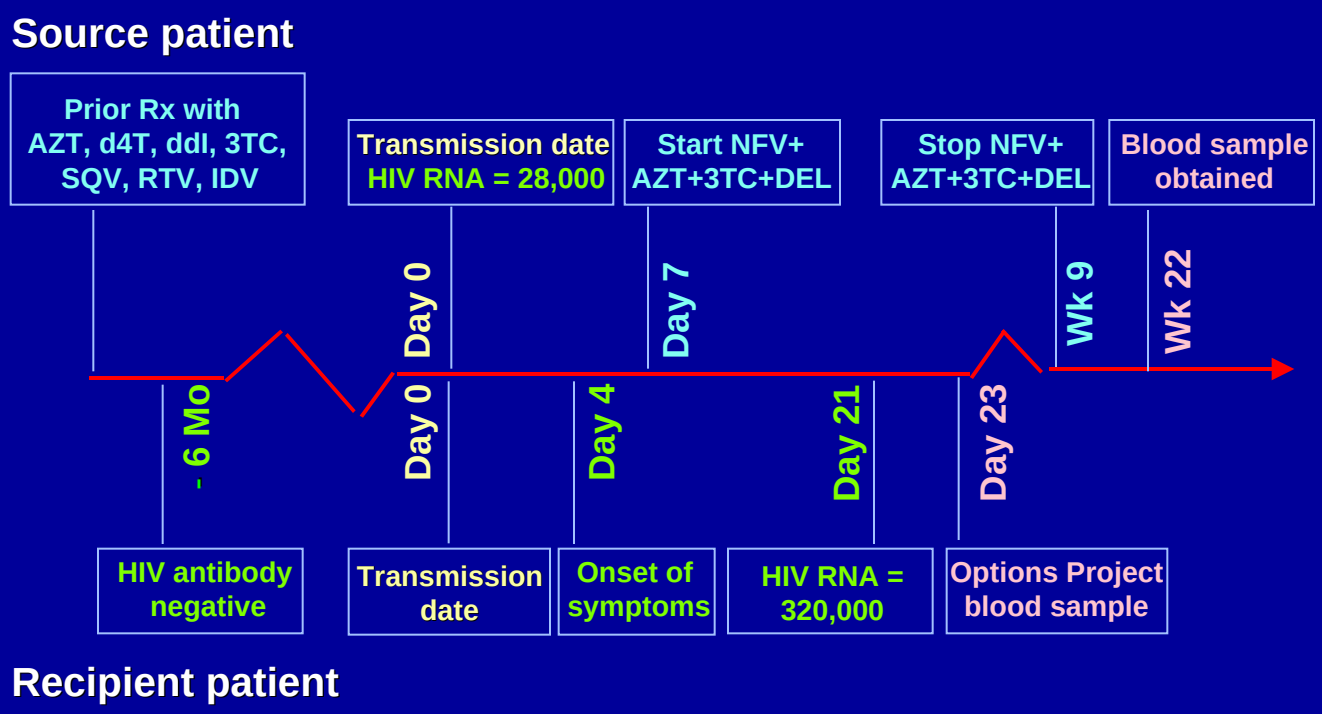
ViroLogic

Treatment Decisions at Time of Treatment Initiation: Important Considerations

- HIV with reduced drug susceptibility has been detected in 2-25% of newly infected and untreated patients
  - Transmission of NRTI, NNRTI, protease, and multi-drug resistant HIV strains have been reported
- First treatment regimen is more likely to produce sustained viral suppression than subsequent regimens
  - Optimization of initial regimen may prolong treatment response

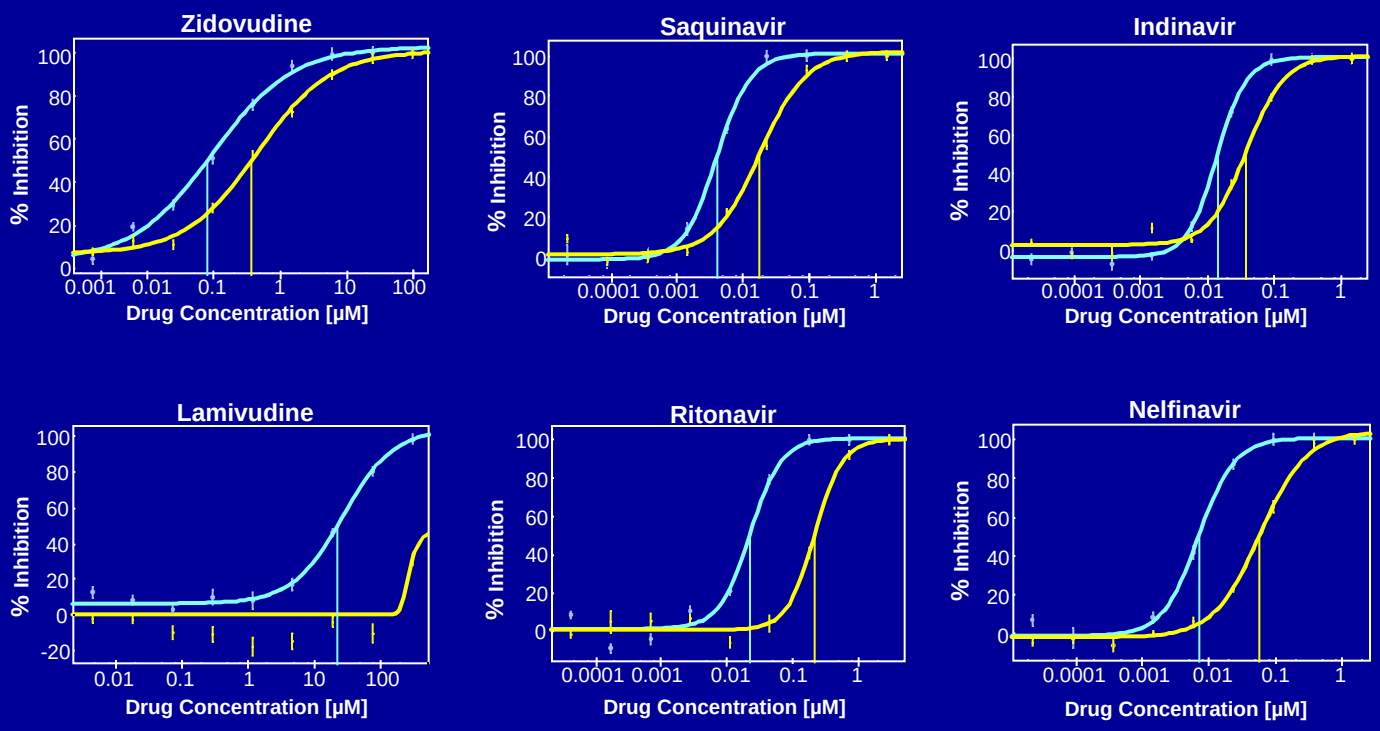
ViroLogic

Transmission of Protease-resistant HIV-1



ViroLogic

Transmission of multidrug-resistant HIV-1: Index patient



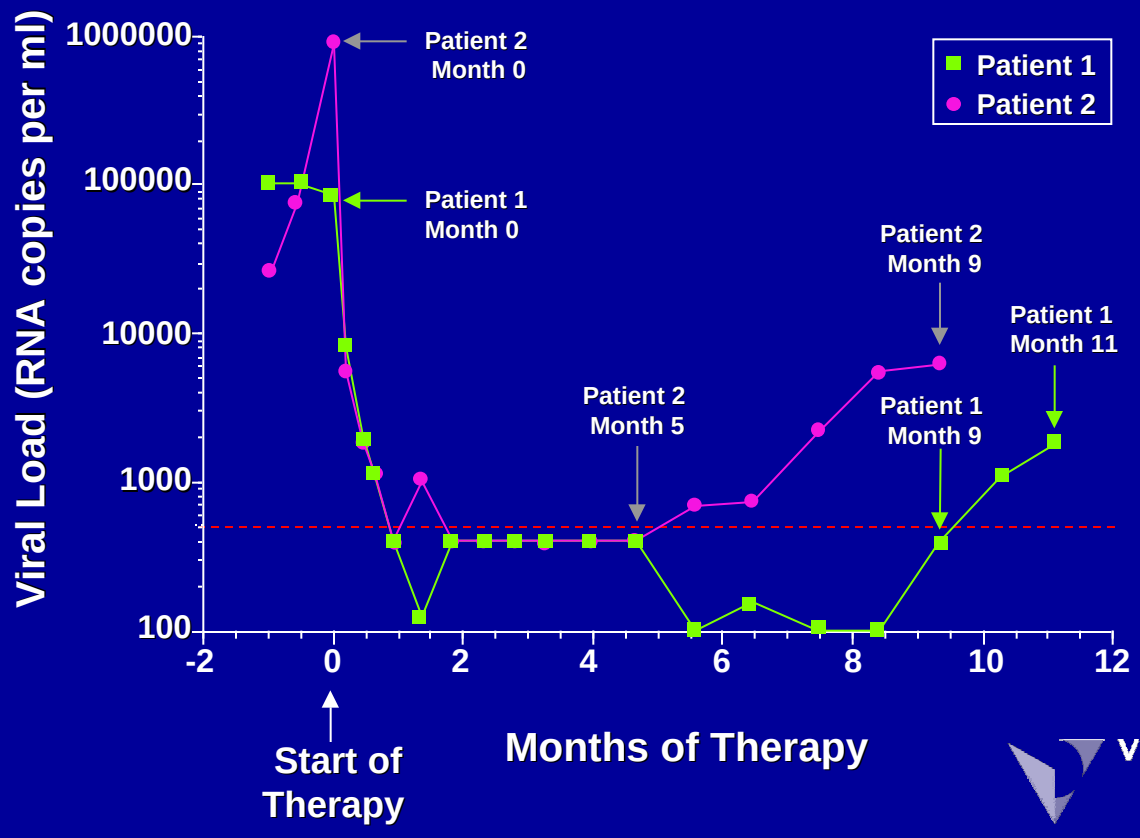
ViroLogic

Potential Clinical Utility of PhenoSense HIV

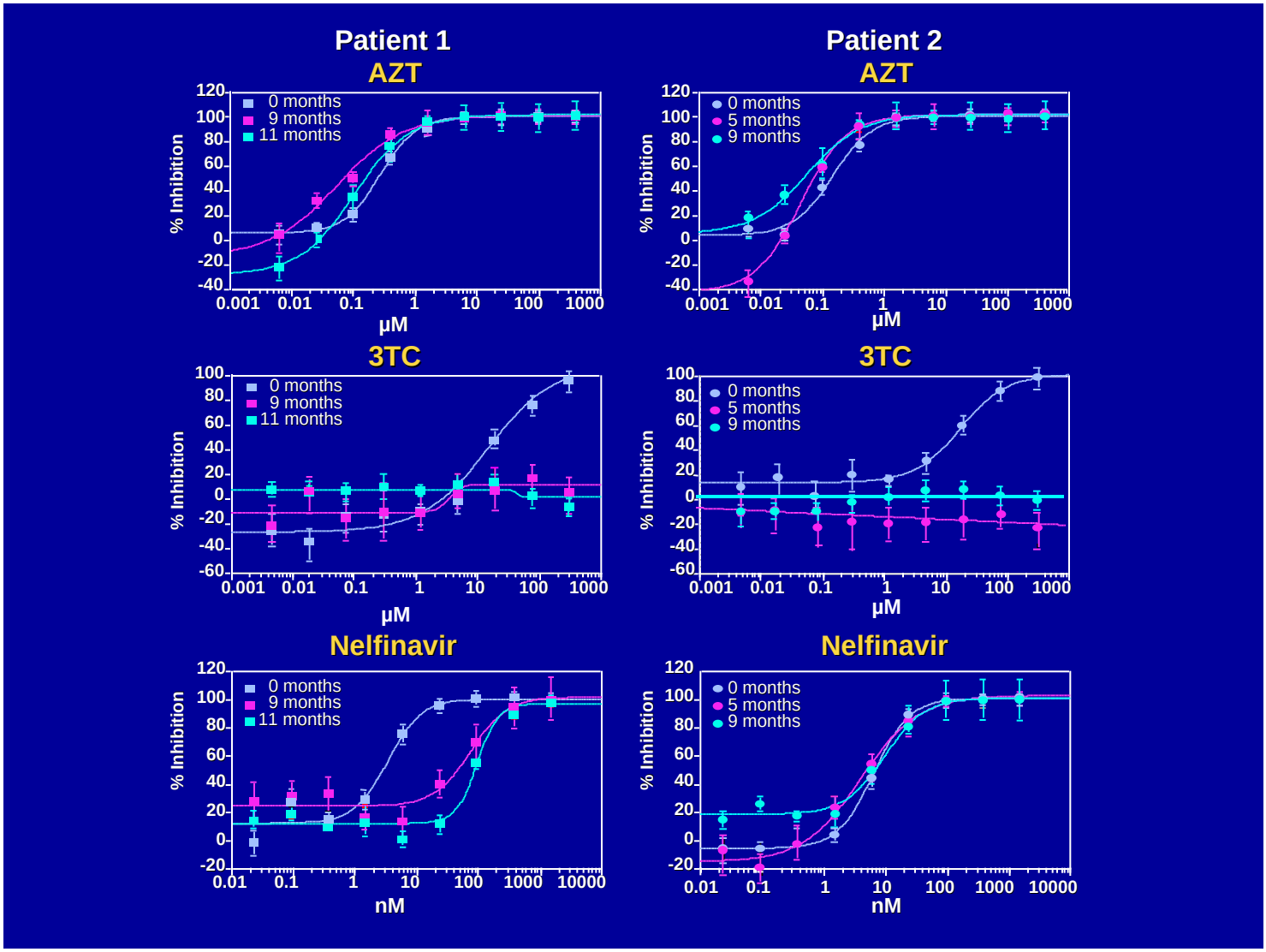
- Treatment decisions after failure of therapy
- Treatment decisions at time of treatment initiation
- **Monitoring for onset of viral resistance**
- Determining optimal treatments in a population

ViroLogic

AZT + 3TC + Nelfinavir: Treatment Failure Viral Load Profile



ViroLogic


Patient 1
AZT
0 months
9 months
11 months
% Inhibition
μM
3TC
Nelfinavir
nM
Patient 2
5 months

Potential Clinical Utility of PhenoSense HIV

- Treatment decisions after failure of therapy
- Treatment decisions at time of treatment initiation
- Monitoring for onset of viral resistance
- **Determining optimal treatments in a population**

ViroLogic

Optimal Treatment in Patient Populations: Some Important Considerations

- Patterns of drug resistance
- Prevalence of drug resistance
- Frequency of resistant virus transmission

ViroLogic

Conclusions

- PhenoSense™ HIV represents a new assay for rapidly (<14 days) providing accurate and reproducible drug susceptibility data to the HIV-treating clinician. Since drug resistance is a major cause of treatment failure in HIV-infected patients, the addition of PhenoSense™ HIV to other clinical tools available for management of HIV infection may permit clinicians to make more rational treatment decisions and select more effective antiretroviral treatment regimens.

ViroLogic