NORTHWEST AIDS EDUCATION AND TRAINING CENTER

CROI 2014: Treatment & Resistance

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No financial conflicts of interest

Outline

- Treatment
  - ATV/r vs RAL vs DRV/r (Abstract # 85)
  - LATTE study (Abstract # 91LB)
- Resistance
  - Transmitted drug resistance (Abstract #87)

ATV/r vs RAL vs DRV/r?

ACTG 5257: Comparison of non-EFV 1st line regimens Background

- **Current recommended 1st line anchors**
  - Atazanavir 300mg qday + ritonavir 100mg qday
  - Raltegravir 400mg bid
  - Darunavir 800mg qday + ritonavir 100mg qday
  - ~~Efavirenz 600mg qday~~

- **Hypothesis:**
  - Regimens would be equal by efficacy and tolerability

Landovitz RJ et al, CROI 2014, Abstract 85

ACTG 5257: Comparison of non-EFV 1st line regimens

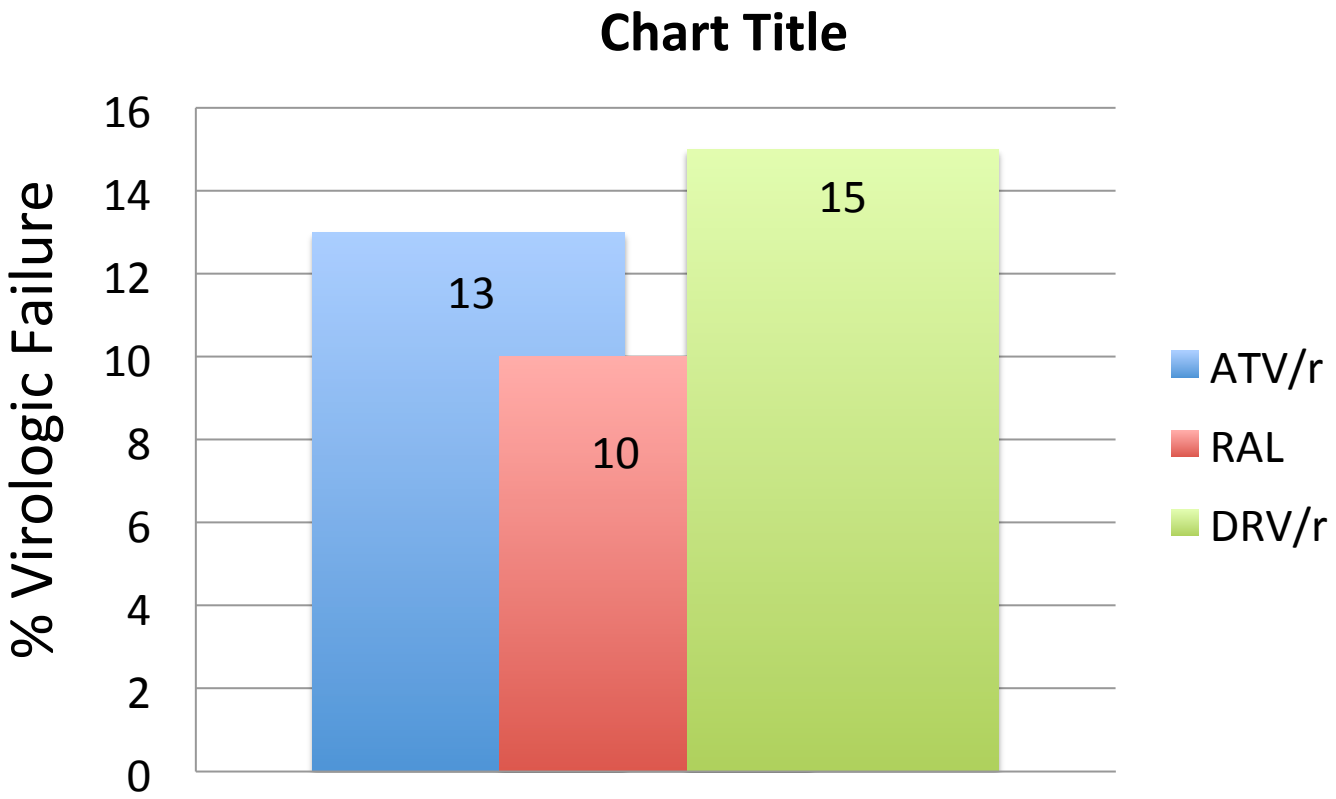
- **Design:**
  - 1:1:1 randomization to ATV/r vs RAL vs DRV/r; 57 sites
  - ~ 600 in each arm
  - Primary endpoint: virologic failure, tolerability failure

- **Baselines characteristics**
  - Similar
  - ~30% had VL > 100K at baseline (7% > 500K)

- **Results:**
  - No differences in virologic failure
  - Differences in tolerability (raltegravir superior)

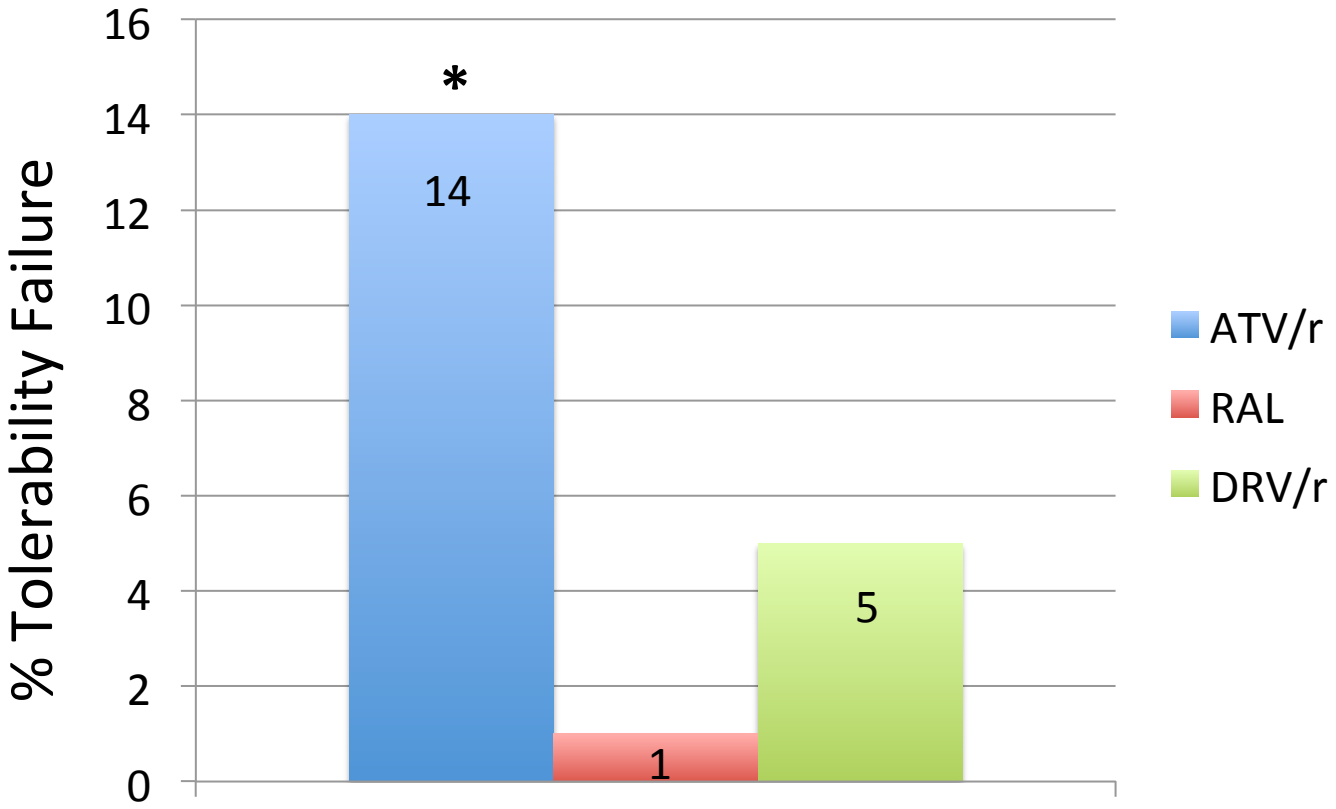
Landovitz RJ et al, CROI 2014, Abstract 85

ACTG 5257: Comparison of non-EFV 1st line regimens Virologic Failure Endpoint at 96 weeks



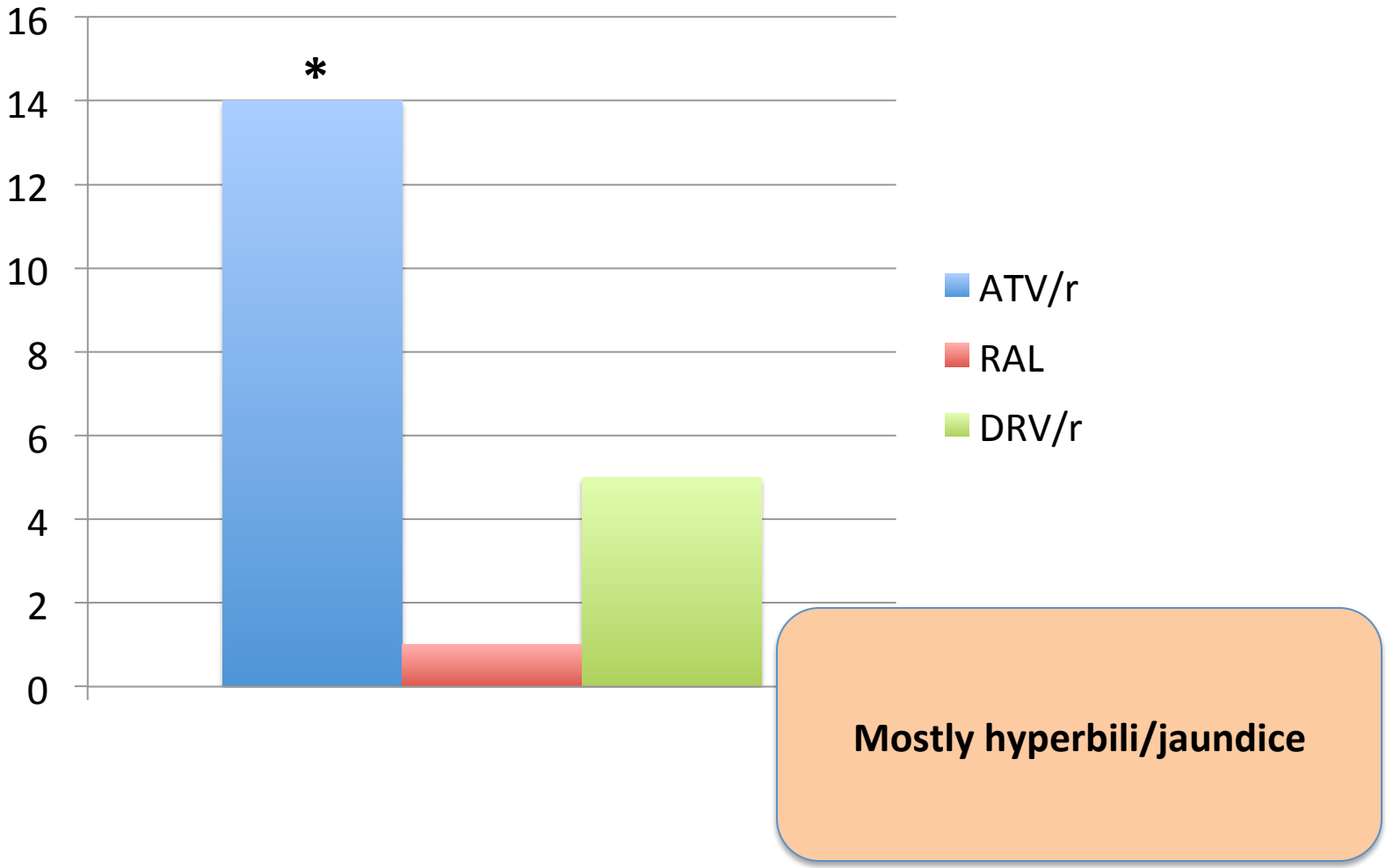
Landovitz RJ et al, CROI 2014, Abstract 85

ACTG 5257: Comparison of non-EFV 1st line regimens Tolerability Failure Endpoint at 96 weeks



Landovitz RJ et al, CROI 2014, Abstract 85

ACTG 5257: Comparison of non-EFV 1st line regimens Tolerability Failure Endpoint at 96 weeks



Landovitz RJ et al, CROI 2014, Abstract 85

ACTG 5257: Comparison of non-EFV 1st line regimens Virologic Failure & Resistance

- **Virologic failure with resistance rare**

  - ATV/r (1.5%)
    - 5 M184V alone
    - 1 integrase
    - 2 T69D
    - 1 K70N + M184V
  - RAL (3%)
    - 7 M184V alone
    - 1 integrase alone
    - 7 integrase + M184V
    - 3 integrase + M184V + K65R
  - DRV/r (< 1%)
    - 3 isolated M184V
    - 1 integrase

Landovitz RJ et al, CROI 2014, Abstract 85

LATTE Study

LATTE Study
Long Acting anTiretroviral Treatment Enabling study

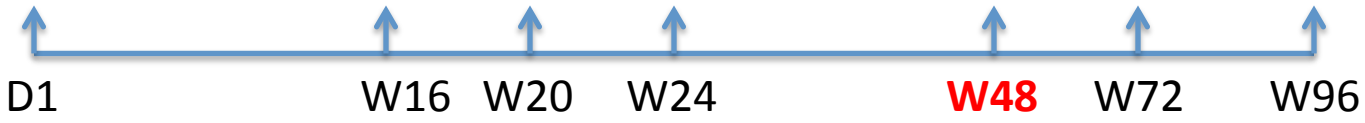
- **Background:**
  - GSK1265744 (744) – dolutegravir analogue
    - Oral drug half-life = 40 hours
    - Long acting SC or IM half-life = 40 days
- **Objectives:**
  - Assess safety, tolerability, and efficacy
  - Results to be used to develop phase 2 study with long-acting drugs

Margolis D et al, CROI 2014, Abstract 91LB

LATTE Study
Long Acting anTiretroviral Treatment Enabling study

- **Design:**
  - Phase IIb, randomized, multicenter, partially blind, dose-ranging study
  - Primary Endpoint: : % HIV-1 RNA < 50c/mL at 48 weeks

Oral Induction Phase	Oral Maintenance Phase
744 10mg + 2 NRTIs	744 10mg + RPV 25mg
744 30mg + 2 NRTIs	744 30mg + RPV 25mg
744 60mg + 2 NRTs	744 60mg + RPV 25mg
EFV 600mg + 2 NRTIs	



Margolis D et al, CROI 2014, Abstract 91LB

LATTE Study
Long Acting anTiretroviral Treatment Enabling study

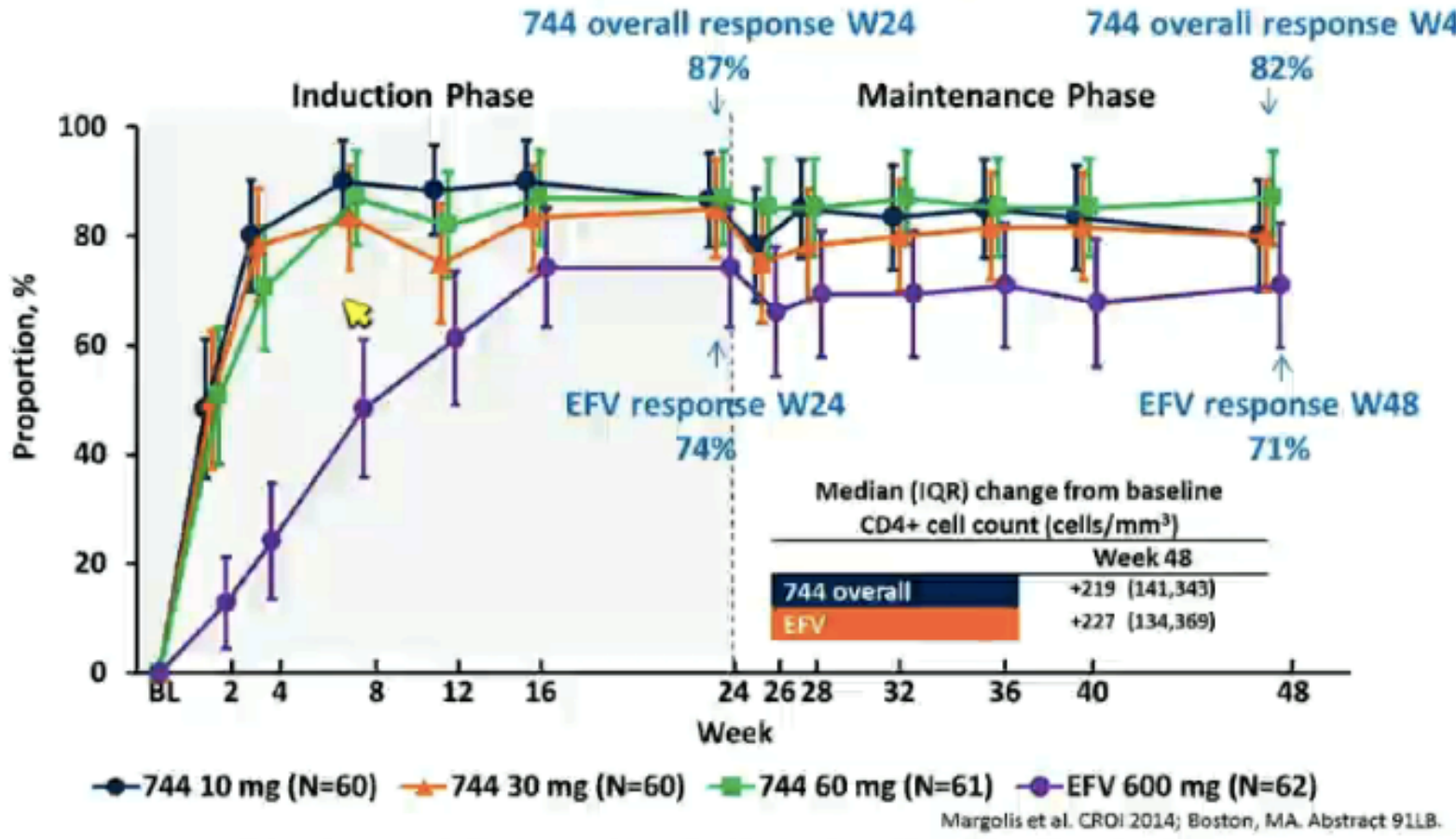
- **Results:**
  - Mostly men (>90%)
  - Withdrawals 15% in composite 744 arms vs. 29% in EFV arm (related to AEs)
  - Induction phase
    - 744 arms – 3 protocol defined failures; EFV – 3 failures
  - Maintenance phase
    - 2 on 744; 1 on EFV
  - Adverse events
    - No AE's related to dose on 744
    - Headache 22% in 744 vs. 11% in EFV
    - Only 1 serious AE (suicide attempt in EFV arm)

Margolis D et al, CROI 2014, Abstract 91LB

LATTE Study
Long Acting anTiretroviral Treatment Enabling study

Primary Endpoint

Virologic Success: HIV-1 RNA <50 c/mL by FDA Snapshot (ITT-E)



Margolis D et al, CROI 2014, Abstract 91LB

LATTE Study
Long Acting anTiretroviral Treatment Enabling study

- **Conclusions:**
  - Next study will use 744 30mg dose and evaluate long-acting formulation with RPV long acting
  - Questions/Concerns about adherence and development of resistance

Margolis D et al, CROI 2014, Abstract 91LB

Sensitive Screening Reveals Widespread Underestimation of Transmitted HIV Drug Resistance

Transmitted Drug Resistance in the US

- **Background:**
  - 14-16% transmitted resistance in US by conventional sequencing
  - Minority level TDR associated with poor treatment outcomes
- **Study:**
  - 1070 de-identified HIV positive ARV-naïve plasma specimens from 2009-2011 from 8 US sites
  - Sensitive mutation specific PCR method to screen for 5 mutations:
    - M41L, K103N, Y181C, M184V, K65R
    - These 5 mutations account for 50% of TDR

Johnson JA et al, CROI 2014, Abstract 87

Transmitted Drug Resistance in the US

- **Results:**
  - 7.9 % TDR by standard sequencing vs. 13.6 % by sensitive testing
  - 5.4 % of "wild-type" cases had TDR by sensitive testing
  - Black 14.8%; White 16.4%; Hispanic 6.4%
  - As age increases, TDR decreases (13-19 y/o 23.1% TDR)
  - 33% of K65R and 58% of M184V transmitted with other mutations

Johnson JA et al, CROI 2014, Abstract 87

Transmitted Drug Resistance in the US

- **Results:**

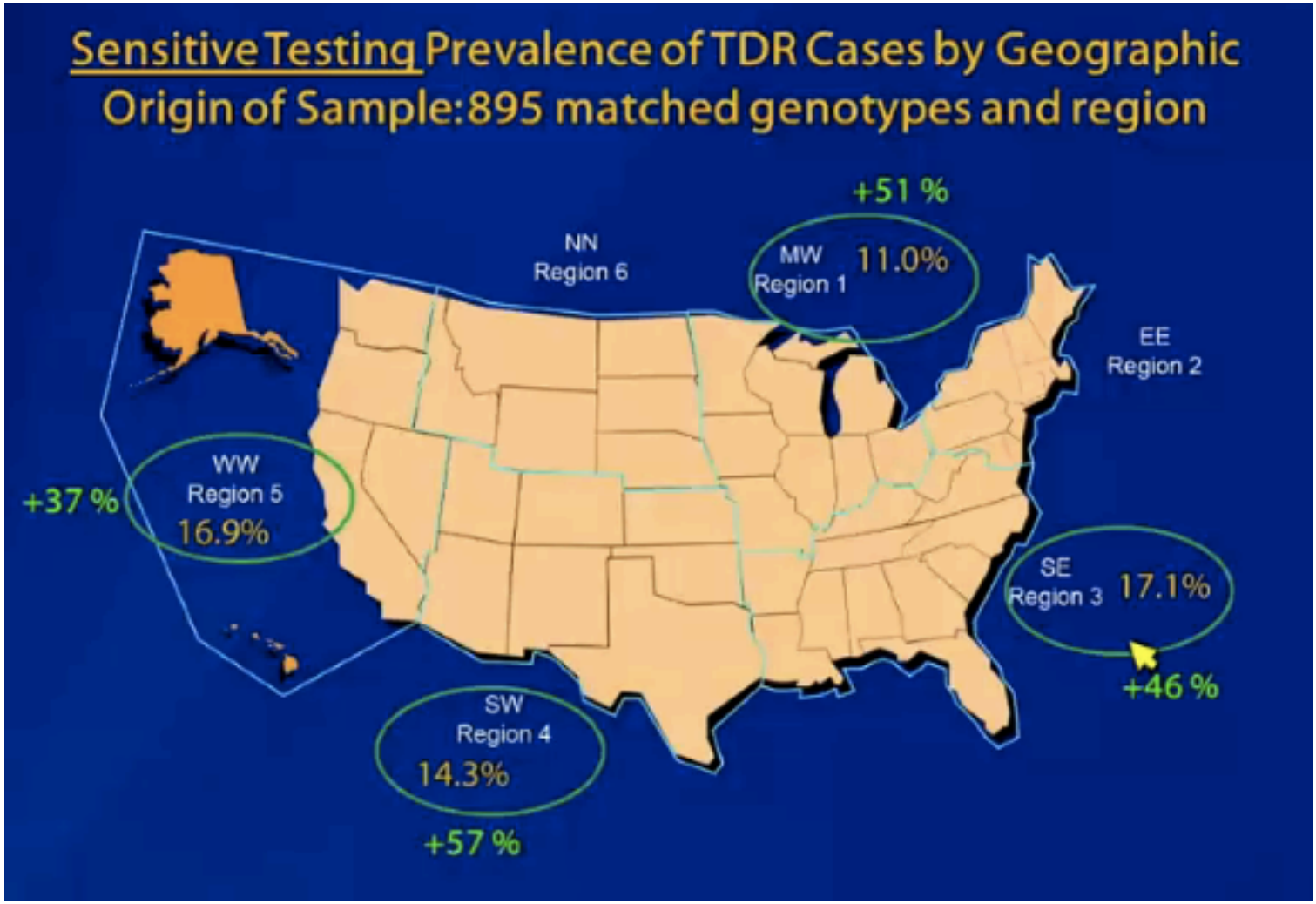
Bulk Genotyping and Sensitive Test Results for 5 Transmitted Drug Resistance (TDR) Mutations in 1070 specimens

Mutation	Bulk Genotype (%)	Sensitive test (%)	% Increase
K65R	0 (0)	18 (1.7)	>340*
K103N	75 (7.0)	90 (8.4)	20
Y181C	9 (0.8)	29 (2.7)	320*
M184V	3 (0.3)	15 (1.4)	500*
M41L	12 (1.1)	15 (1.4)	30
Cases of TDR	85 (7.9)	145 (13.6)*	70

* P <0.0001

Johnson JA et al, CROI 2014, Abstract 87

Transmitted Drug Resistance in the US



Johnson JA et al, CROI 2014, Abstract 87

Transmitted Drug Resistance in the US

- **Conclusions:**
  - Implications for prevention (PrEP) and treatment?

Johnson JA et al, CROI 2014, Abstract 87