Differential Detection of M184V/I Between Plasma Historical HIV Genotypes and Proviral DNA from PBMCs

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HIV Resistance Testing and Antiretroviral Therapy

Plasma Resistance Testing - RAM?

No Treatment | Treatment A | Treatment B

Plasma Resistance Testing - RAM?

HIV-1 RNA (copies/mL)

0 1 2 3 6 7

HIV-1 RNA (copies/mL)

RAM: resistance-associated mutation; VL: HIV-1 RNA viral load
**Suppressed Patients**

**Resistance Testing**

**Treatment Switch (VL<50 c/mL)**

### Resistance Associated Mutations

- Prior Virologic Failure (VF)
  - i.e. M184V/I, 40-50% patients w/VF
    - (high-level resistance to 3TC and FTC and low-level resistance to ABC)

- Transmitted Drug Resistance
  - K103N, TAMs

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**HIV DNA Resistance Testing**

- Integrated Virus

**Study 1824: CRO selected**

*validated assay*

- Hospital laboratory
- Monogram
- Quest
- SeqIT

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*Miller et al AVT, 2012*

*Margot et al JID, 2017*

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*CRO: contract research organization; TAM: thymidine-analog mutation*
Study 1824
Switch Study

- HIV-1-infected Adults
- Switch from 2 NRTIs + 3rd agent
- HIV-1 RNA < 50 c/mL
- Historical Genotype showing M184V/I
  - Part 1: M184V/I only
  - Part 2: M184V/I ±0-2 TAMs
- No exclusionary mutation in HIV DNA analysis

E/C/F/TAF QD
N = 63

12 weeks Primary Endpoint*
24 weeks Secondary Endpoint**
48 weeks

(*) Perez-Valero IDRW, 2017
(**) Perez-Valero WorldAIDS, 2018
100% Suppression using Pure Virologic Failure

Historical reports (local lab and commercial sources)
GenoSure Archive (Monogram)

E/C/F/TAF: single-tablet regimen containing elvitegravir (E), cobicistat (C), emtricitabine (FTC, F), tenofovir alafenamide (TAF)
NRTI: nucleotide reverse transcriptase inhibitor; 3TC: lamivudine
Detection of M184V or I (N=87)
Historical report vs. Archive

- Paired historical & Archive data available for 87 screened patients

<table>
<thead>
<tr>
<th>Genotype</th>
<th>“Historical” (plasma; N=87)</th>
<th>“Archive” (HIV DNA; N=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M184V</td>
<td>78%</td>
<td>38%</td>
</tr>
<tr>
<td>M184I</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td>M184V/I</td>
<td>11%</td>
<td>7%</td>
</tr>
<tr>
<td>Assay Failure</td>
<td>N/A</td>
<td>8%</td>
</tr>
<tr>
<td>WT</td>
<td>N/A</td>
<td>44%</td>
</tr>
</tbody>
</table>

- Archive: Mutation detected in only 48% patients
Presence of M184V and M184I
Historical report vs. Archive

- **M184V Patients (N=69):**
  - 48% detected with Archive

- **M184I Patients (N=9):**
  - 33% detected with Archive

- **M184V:** detected with Archive in 48% patients
- **M184I:** detected with Archive in 33% patients
Detection of M184V/I in Archive Assay
Lack of Detection due to Time from Historical to Archive Sample?

- Differential detection not due to sample timing or time on ART

**ART:** antiretroviral therapy; **H:** historical genotypic report (plasma); **A:** Archive genotypic report (HIV DNA); (*) Mann Whitney test
Detection of M184V/I in Archive Assay
ART Regimen at Baseline (n=78)

- Differential detection not associated with baseline regimen

INSTI: integrase strand transfer inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor
Detection of M184V/I in Archive Assay
Lack of Detection Linked to CD4 Cell Count or HIV-1 RNA?

- Differential detection not associated with Baseline CD4 count or viral load

TND: target not detected; VL: Viral load; (*) Mann Whitney test
Conclusions

- In subjects with documented prior M184V/I on historical genotype
  - M184V not detected in 52% with Archive assay
  - M184I not detected in 67% with Archive assay (A3G?)

- Difference in detection of M184V/I not associated with:
  - Time between historical and archived testing
  - Time on ART
  - Prior treatment regimen
  - Baseline CD4 count
  - HIV-1 RNA detection (TND, <20, <50)

- Not detecting M184V/I may have potential clinical consequences when switching patients to 2-drug treatment containing FTC or 3TC
  - Presence of M184V/I confers high-level resistance to FTC and 3TC
Acknowledgments

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