Disclaimer

_Presentation includes investigational drugs not approved for use outside of clinical trials_
Integrase Inhibitors

- Raltegravir (RAL)
- Elvitegravir (EVG)
- Dolutegravir (DTG)
- Cabotegravir - Investigational – data accumulating
- Bictegravir (BIC) – Investigational – preliminary data only
Integrate Inhibitors

• Raltegravir (RAL)
• Elvitegravir (EVG)
• Dolutegravir (DTG)
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Resistance characteristics are substantially different
Between first and second generation integrase inhibitors
Integrase Inhibitors

Raltegravir

Elvitegravir

Dolutegravir

Bictegravir
Dolutegravir
Bictegravir
Cabotegravir
Integrase Inhibitors – Second Generation

Cabotegravir

Dolutegravir

Bictegravir
Integrase Inhibitor in Active Site

RCSB Protein Data Base
Integrase Inhibitor in Active Site

RCSB Protein Data Base
Key Raltegravir Mutations
DTG versus RAL Alignment in Active Site
Dolutegravir

- Dolutegravir was developed specifically to have improved resistance characteristics
- The structure was continually changed to improve resistance characteristics (reducing fold change of resistance mutations)
# Optimizing the Scaffold Against a Key Mutant

<table>
<thead>
<tr>
<th>Series</th>
<th>IC$_{50}$ (nM) wt</th>
<th>Q148K Resistance (fold)</th>
<th>Protein Shift (fold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-1.</td>
<td>3</td>
<td>48x</td>
<td>16.8x</td>
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<tr>
<td>B-2.</td>
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<td>29x</td>
<td>3.1x</td>
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<tr>
<td>C-1.</td>
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<td>3.7x</td>
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<tr>
<td>D-1.</td>
<td>5</td>
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<td>7.9x</td>
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17th Conference on Retroviruses and Opportunistic Infections, 16–19 February 2010, San Francisco, CA, USA
Mean FC of Site Directed Mutants identified During Passage with Wild-type Virus in the Presence of S/GSK1349572

<table>
<thead>
<tr>
<th>Viruses</th>
<th>Mean FC</th>
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<tbody>
<tr>
<td>S/GSK1349572</td>
<td></td>
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<tr>
<td>S153F</td>
<td>1.6</td>
</tr>
<tr>
<td>S153Y</td>
<td>2.5</td>
</tr>
<tr>
<td>L101I/S153F</td>
<td>2.0</td>
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<tr>
<td>L101I/T124A/S153F</td>
<td>1.9</td>
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</table>

Adapted from Seki et al, CROI 2010
RESISTANCE OF INTEGRASE MUTATIONS TO DIFFERENT INTEGRASE INHIBITORS

EC₅₀, 50% effective concentration

*Not tested for EVG

1. Adapted from Seki T, et al. CROI 2010. Poster J-122
Genetic Barrier to Resistance:
Virology and Pharmacology
Genetic Barrier to Resistance: Virology and Pharmacology

Plasma concentration of Drug

Drug level

Time (hours)
Genetic Barrier to Resistance: Virology and Pharmacology

Drug level to inhibit WT virus

Plasma concentration of Drug

Time (hours)
Genetic Barrier to Resistance: Virology and Pharmacology

Drug level to inhibit WT virus

Plasma concentration of Drug

Minimal Plasma level of drug (Cmin)

Time (hours)

0 2 4 6 8 10 12
Estimating the Barrier to Resistance

Minimal Plasma level of drug ($C_{\text{min}}$)

Drug level to inhibit WT virus
Estimating the Barrier to Resistance

Minimal Plasma level of drug ($C_{\text{min}}$)

Drug level to inhibit WT virus
Estimating the Barrier to Resistance

Minimal Plasma level of drug (Cmin)

Is this the clinically relevant Genetic Barrier to Resistance?

Drug level to inhibit WT virus
Correcting for Protein Binding of Drug in Plasma

Minimal Plasma level of drug \((C_{\text{min}})\)

Drug level to inhibit WT virus
Correcting for Protein Binding of Drug in Plasma

Minimal Plasma level of drug (Cmin)

Drug level to inhibit WT virus corrected for protein binding

Drug level to inhibit WT virus
Estimating the Barrier to Resistance

Minimal Plasma level of drug (Cmin)

What is Missing?

Drug level to inhibit WT virus corrected for protein binding

Drug level to inhibit WT virus
How Much Resistance from a Single Mutation to the Drug

- Minimal Plasma level of drug ($C_{\text{min}}$)
- Drug level to inhibit most potent single mutation to the drug
- Drug level to inhibit WT virus corrected for protein binding
- Drug level to inhibit WT virus
How Much Resistance from a Single Mutation to the Drug

Minimal Plasma level of drug ($C_{\text{min}}$)

Drug level to inhibit most potent single mutation to the drug

Drug level to inhibit WT virus corrected for protein binding

Drug level to inhibit WT virus
Estimating the Barrier to Resistance

Minimal Plasma level of drug ($C_{\text{min}}$)

Drug level to inhibit most potent single mutation to the drug

Drug level to inhibit WT virus corrected for protein binding

Drug level to inhibit WT virus
Drug level to inhibit WT virus

Minimal Plasma level of drug (Cmin)

Drug with potentially **high** genetic barrier to resistance

Drug level to inhibit most potent single mutation to the drug

Drug level to inhibit WT virus corrected for protein binding

Drug level to inhibit WT virus
Estimating the Barrier to Resistance

- Drug level to inhibit most potent single mutation to the drug
- Minimal Plasma level of drug (Cmin)
- Drug level to inhibit WT virus corrected for protein binding
- Drug level to inhibit WT virus
Estimating the Barrier to Resistance

Drug level to inhibit most potent single mutation to the drug

Minimal Plasma level of drug (Cmin)

*Drug with potentially Low genetic barrier to resistance*

Drug level to inhibit WT virus corrected for protein binding

Drug level to inhibit WT virus
Factors Contributing to a High Genetic Barrier to Resistance

- Minimal Plasma level of drug ($C_{min}$)
- Drug level to inhibit most potent single mutation to the drug
- Drug level to inhibit WT virus corrected for protein binding
- Drug level to inhibit WT virus

*Potentially High Genetic Barrier*

Fold Change Resistance of Single Mutant = 3
Factors Contributing to a High Genetic Barrier to Resistance

- Fold Change Resistance of Single Mutant = 30
- Potentially Low Genetic Barrier

- Drug level to inhibit WT virus corrected for protein binding
- Minimal Plasma level of drug (Cmin)
- Drug level to inhibit most potent single mutation to the drug
Structure of Protease Inhibitor Darunavir
Structure of Protease Inhibitor Amprenavir
Structure of Protease Inhibitor Amprenavir
Structure of Protease Inhibitor Darunavir
### Darunavir versus Amprenavir Resistance: Fold Change to Identical Mutations

<table>
<thead>
<tr>
<th>PI</th>
<th>DRV/r (130)</th>
<th>FPV/r (320)</th>
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</thead>
<tbody>
<tr>
<td>V32I</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>L33F</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>I54L</td>
<td>20</td>
<td>60</td>
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<tr>
<td>I84V</td>
<td>15</td>
<td>60</td>
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<tr>
<td>I50V</td>
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<tr>
<td>L76V</td>
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<td>60</td>
</tr>
<tr>
<td>L89V</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>
Genetic Barrier to Resistance DRV/r 600/100 BID

Minimal Plasma level of drug (Cmin)

DRV/r Genetic Barrier to Resistance

Drug level to inhibit most potent single mutation to the drug

Drug level to inhibit WT virus corrected for protein binding

Drug level to inhibit WT virus
Genetic Barrier to Resistance LPV/r 400/100 BID

Minimal Plasma level of drug (Cmin)

LPV/r Genetic Barrier to Resistance

Drug level to inhibit most potent single mutation to the drug

Drug level to inhibit WT virus corrected for protein binding

Drug level to inhibit WT virus
Estimated Genetic Barrier of Efavirenz

Drug level to inhibit most potent single mutation to the drug

Minimal Plasma level of drug (Cmin)

Low Genetic Barrier Drug

Drug level to inhibit WT virus corrected for protein binding

Drug level to inhibit WT virus
Resistance Characteristic of Integrase Inhibitors

Clinical Significance
Resistance Accumulation in Patients Failing First Generation Integrase Inhibitors
Do Resistance Mutations Accumulate Over Time if Patients Have Low Level Viremia?
Impact of Low-Level-Viremia on HIV-1 Drug-Resistance Evolution among Antiretroviral Treated-Patients

Constance Delaugerre¹,²,³, Sébastien Gallien²,³,⁴, Philippe Flandre⁵,⁶, Dominique Mathez⁷, Rishma Amarsy¹, Samuel Ferret⁴, Julie Timsit⁸, Jean-Michel Molina²,³,⁴, Pierre de Truchis⁹

Impact of Low-Level-Viremia on HIV-1 Drug-Resistance Evolution among Antiretroviral Treated-Patients

- 48 highly-treatment experienced patients, on salvage regimens
  - 2 NRTI + PI/r +/- NNRTI and or RAL
- LLV defined as HIV RNA 50 – 500 copies on at least 3 occasions over 6 months or more (Mean follow up 11 months)
- Resistance testing done on first and last HIV RNA test
- Accumulation of additional mutations during LLV determined
Accumulation of Mutations at HIV RNA Below 500 copies
Accumulation of Mutations at HIV RNA Below 500 copies

10% developed new major DRV MU
Accumulation of Mutations at HIV RNA Below 500 copies

2 of 9 developed major RAL MU

Resistance-associated mutations to antiretroviral drugs
Resistance to Second Generation Integrase Inhibitors

• Despite their high genetic barrier, second generation integrase inhibitors are not immune to resistance

• When given with 2 NRTI’s in drug naïve patients, current data suggest using DTG will avoid failure with integrase resistance

• But one must be cautious in extrapolating to all other clinical scenarios
  – Mono or dual therapy
  – Treatment experienced patients
  – Other investigational second generation inhibitors
Resistance to Second Generation Integrase Inhibitors in Investigational Settings
Integrase Inhibitors

Dolutegravir

Cabotegravir
Resistance to Single Integrase Mutations
## Fold Change in IC50 Compared With WT for CAB, DTG, RAL and EVG Against Site-Directed Mutant HIV-1

<table>
<thead>
<tr>
<th></th>
<th>CAB</th>
<th>DTG</th>
<th>RAL</th>
<th>EVG</th>
</tr>
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<tbody>
<tr>
<td>Y143C</td>
<td>1.1</td>
<td>0.95</td>
<td>3.2</td>
<td>1.5</td>
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<td>Y143H</td>
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<td>0.89</td>
<td>1.8</td>
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<tr>
<td>Y143R</td>
<td>1.4</td>
<td>1.4</td>
<td>16</td>
<td>1.8</td>
</tr>
<tr>
<td>Q148H</td>
<td>0.86</td>
<td>0.97</td>
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<td>Q148K</td>
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<tr>
<td>Q148R</td>
<td><strong>5.1</strong></td>
<td><strong>1.2</strong></td>
<td><strong>47</strong></td>
<td><strong>240</strong></td>
</tr>
<tr>
<td>N155H</td>
<td>0.99</td>
<td>1.2</td>
<td>11</td>
<td>25</td>
</tr>
</tbody>
</table>

- While CAB has ~4 higher FC IC50 for Q148R compared with DTG, CAB remains 9-fold to 47-fold more active than RAL and EVG, respectively.
Once-Daily Oral GSK1265744 (744) as Part of Combination Therapy in Antiretroviral-Naive Adults: 24-Week Safety and Efficacy Results From the LATTE Study (LAI116482)

David Margolis, 1 Laveeza Bhatti, 2 Graham Smith, 3 Winkler Weinberg, 4 Cynthia Brinsson, 5 Tony Mills, 6 Edwin DeJesus, 7 Britt Stancil, 1 Paul Wannamaker, 1 Melinda Bomar, 1 Marty St Clair, 1 William Sreen, 1 James Goodrich 8

1 GlaxoSmithKline, Research Triangle Park, NC, USA; 2 AIDS Healthcare Foundation, Beverly Hills, CA, USA; 3 Maple Leaf Medical Clinic, Toronto, Canada; 4 Kaiser Permanente, Atlanta, GA, USA; 5 Central Texas Clinical Research, Austin, TX, USA; 6 Anthony Mills MD Inc, Los Angeles, CA, USA; 7 Orlando Immunology Center, Orlando, FL, USA; 8 ViiV Healthcare, Research Triangle Park, NC, USA
LATTE Study Design

- Phase IIb, randomized, multicenter, partially blind, dose-ranging study
- 744 + NRTI subjects with a W20 HIV-1 RNA <50 c/mL simplified to 744 + RPV at W24

**Oral Induction Phase**
- 744 10 mg + 2 NRTIs*
- 744 30 mg + 2 NRTIs
- 744 60 mg + 2 NRTIs

**Oral Maintenance Phase**
- 744 10 mg + RPV 25 mg
- 744 30 mg + RPV 25 mg
- 744 60 mg + RPV 25 mg

HIV ART-naive
HIV-1 RNA >1000 c/mL
1:1:1:1 Randomization
Stratified by VL and NRTI

*ABC/3TC or TDF/FTC

Primary endpoint: % HIV-1 RNA <50 c/mL at 48 weeks ("FDA Snapshot")
Virologic Success: HIV-1 RNA <50 c/mL (ITT-E)

Margolis DA et al, CROI Feb 2015, Seattle
Profile of a Single Subject With Treatment-Emergent Resistance on 10 mg CAB

- CAB 10 mg + RPV 25 mg (NNRTI)
- Low CAB and RPV plasma drug concentrations
- Severe diet (650 kcal/day) between W40 and W48

HIV-1 RNA (c/mL)

- CAB + TDF/FTC
- CAB + RPV
- Q148R IN E138Q RT

CAB or RPV C₀ (ng/mL)

- CAB 10 mg
- RPV 25 mg

Dudas K et al. IWADR Feb 2015, Seattle
Resistance to Investigational Second Generation Integrase Inhibitors – Clinical Validation

- Data generated from multiple large clinical trials and widespread routine use are available only for 2 NRTI + DTG on lack of failure with resistance.
- Both Cabotegravir and Bictegravir currently lack such data.
- Initial results are promising but require further validation.
- Only after these drugs have been used in widespread clinical settings will we know if they possess similar resistance characteristics.
Dolutegravir (DTG) monotherapy treatment de-escalation in virological controlled, pre-treated HIV patients: Results from the DoluMono cohort study

Celia Oldenbüttel et al

HIV Drug Therapy, October 2016, Glasgow UK
DoluMono cohort study

• Retrospective cohort study from single center
• Patients on suppressive ART, undetectable at least 6 months, who were switched to DTG monotherapy as part of routine clinical practice
• Could have no prior integrase inhibitor failure or resistance
• 31 patients with 24 week follow up identified
• 94% remained <50 copies on DTG monotherapy
• One virological failure with integrase resistance
• HIV RNA: 538, Integrase mutations: G140 S+ Q148H
Integrase Inhibitors: Surveillance for Transmitted Resistance

• Surveillance for increasing levels of transmitted integrase resistance is key in determining if and when integrase genotyping will be required for newly infected patients.

• Taiwan reported an INI resistance prevalence of 1.2% for integrase inhibitor naïve patients a number of years after RAL was introduced to the country.

• This may be due to practices of RAL use – and is being addressed.

• Prevalence of integrase mutations in naïve patients may depend on a number of factors.
Factors Impacting the Prevalence of INI Mutations

- Drugs used (RAL, EVG vs. DTG)
- Regimen used (triple, dual or monotherapy)
- Frequency of HIV RNA viral load monitoring
- Thresholds for acting on detectable HIV RNA results
- Availability of integrase resistance testing
Summary

• First and second generation integrase inhibitors have diverse resistance characteristics
• Despite all being very potent drugs, this has implications for their optimal clinical use
• Transmitted integrase resistance may likely have a greater impact on first, than on second generation agents
• Continuous surveillance for integrase transmitted drug resistance is of high importance, certainly where first generation drugs are commonly used
Summary

• First and second generation integrase inhibitors have diverse resistance characteristics
• Despite all being very potent drugs, this has implications for their optimal clinical use
• Transmitted integrase resistance may likely have a greater impact on first, than on second generation agents
• Continuous surveillance for integrase transmitted drug resistance is of high importance, certainly where first generation drugs are commonly used
Summary II

• Patients receiving first generation integrase inhibitors need to be monitored for failure, as mutations can quickly accumulate reducing or negating the use of second generation drugs

• Tolerating low level viremia in patients on first generation drugs (first line or salvage) – may lead to loss of subsequent second generation option

• To date, convincing evidence for the lack of resistance upon failure of a second generation integrase inhibitors is available only for DTG in the context of a 2 NRTI regimen

• All other regimens, drugs and scenarios requires further study with sufficient numbers and follow-up
Thank You