Complete Failure of RTV/SQV to Suppress HIV Replication

Patients with Baseline HIV RNA > $10^5$ copies/mL

Proportion < 400 copies/mL HIV RNA

- RTV/SQV/d4T n=29
- RTV/SQV n=16
Complete Failure of RTV/SQV to Suppress HIV Replication

- Prometheus trial results
- 28 patients in the RTV/SQV arm required intensification (vs. 3)
  - 21 with d4T/3TC
- 15 because they had > 400 copies/ml at 12 and 18 weeks
- 4 because > 1000 copies/ml at 12 weeks
- 7 because of HIV RNA rebound
Superior Freedom From Lipodystrophy with RTV/SQV Alone

Antiretroviral Drug Naïve Subjects

Proportion Free From Lipodystrophy

$\rho = 0.009$

Weeks
Positive Pharmacokinetic Interaction Between SAQ/Kaletra

Median saquinavir concentration (log [ng/ml])

Sample time (h)

SQV / LPV / r
1000/400/100 mg bid

SQV / r
1000/100 mg bid

Stephan et al. XIV IAC 2002; poster TuPe4561
Protease Inhibitor Experienced (PIE) Study of SQV/Kaletra

• Design: pilot study for safety and activity
• Regimen: optimized NRTIs plus
  – SQV (FTV or INV) 1000 mg bid
  – LPV/r 400/100 mg bid
• Population: n=28
  – All PI-experienced
  – LPV-naive

Hellinger et al., 2nd IAS 2003; abstract 571
Double Boosted SAQ/LPV Suppresses HIV in PI Experienced Patients

From baseline (log)

Weeks

0.50
0.00
-0.50
-1.00
-1.50
-2.00
-2.50

12 16 20 24

Change from baseline (log)

ITT n=28
OT n=28

Hellinger et al. 9th CROI, 2002; poster 451-W
PIN Study: SQV/LPV/r without RTIs in PI naive patients

• Pilot study (n=20) to assess safety and activity of SQV 1000 mg bid with LPV/r 400/100 mg bid
  • NRTI intensification after week 12 as needed

• Baseline data:
  • CD4 median 274
  • Viral load 4.1 log

Hellinger et al, 2nd IAS 2003; abstract 571
Double Boosted PI in Naïve Patients: Well Tolerated

<table>
<thead>
<tr>
<th>Total n (%)</th>
<th>Initiated study medication</th>
<th>Completed week 48</th>
<th>Intensification with NRTI</th>
<th>Discontinued prior to week 48</th>
<th>Reasons for discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20</td>
<td>16</td>
<td>2 (10%)</td>
<td>4 (20%)</td>
<td>Clinical adverse event: 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non adherence/ “pill fatigue” : 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Moved residence: 1</td>
</tr>
</tbody>
</table>

Hellinger et al., 2nd IAS 2003; abstract 571
Suppression of HIV Replication with Double Boosted PIs in Naïve PI Patients

Hellinger et al., 2nd IAS 2003; abstract 571
All Blue Skies and Smiles in “The City by The Bay”
All Blue Skies and Smiles in “The City by The Bay”

- Entry Inhibitors Take Center Stage
- Numerous companies now in the clinic: Merck, Glaxo, Pfizer, BMS, Schering, plus others
- Phase I and Ib data looks promising for Schering D (SCH 417690) compound
- Cardiac and other toxicities are not class specific
- New in vitro model allows for rapid development of many new compounds should existing ones fail
Potential Sites for Blocking HIV Entry and Fusion

Binding of gp120/CD4 allows CCR5 or CXCR4-V3 loop interaction

Cleavage of gp160 into gp120/41 allows shedding and fusion to start

- CCR5 or CXCR4
- V3 Loop
- gp120
- CD4

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Potential Sites for Blocking HIV Entry and Fusion

- CCR5 or CXCR4
- V3 Loop
- gp120
- CD4

Inhibitors:
- BMS-043
- CCR5 or CXCR4 Inhibitors
- T-20 or T-1249
CCR5/CXCR4 Inhibitors Block HIV Entry

Disrupt V3-Chemokine Receptor Interaction

CCR5 or CXCR4 Inhibitors

Merck
AMD070
AMD877
SCH-D
UK427,857
GW873140

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Inhibition of HIV by SCH-D

- 48 patients chronically infected with HIV
- Sequential, escalating dose study of SCH-D
  - 10 mg, 25 mg and 50 mg BID for 14 days
- 12 patients randomly received SCH-D and four patients received placebo
- No antiretroviral treatment for at least eight weeks prior to enrollment and
- CD4+ cell count > 250, HIV RNA 5-200K

Laughlin et al., 2004 11th Retro. Conf. & OI
Inhibition of HIV by SCH-D

- SCH-D was safe and well tolerated at all dose levels
- No drug-specific toxicity
  - 25 mg cohort MAC, syphilis and CVA
- Dose related decreases in viral load
- $T_{1/2}$ exceeds 8 hours
- Susceptibility to SCH-D (BL, 7, 14 and 28d) showed no change
- Mixed results in patients with R5:X4 mixture
  - One with 0.5 log10 reduction
  - One subject (>1.5 log10 reduction during dosing) with transient detection of X4 following cessation
Superior Potency of SCH-D Relative to SCH-C in HIV Infection

Mean IC Values (nM)

- IC50
- IC90

n= 52

* * p <0.001

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Laughlin et al., 2004 11th Retro. Conf. & OI
Schering D Reduces HIV RNA Within Days

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Laughlin et al., 2004 11th Retro. Conf. & OI
T_{1/2} of SCH-D Exceeds 8 Hours
Plasma Levels Easily Maintained Above IC_{90}

Laughlin et al., 2004 11th Retro. Conf. & OI
Resistance to CCR5 Antagonists

- Virus passed in increasing concentrations of SCH-C
- Resistant phenotype became by passage 24
- All subsequent viruses were cross-resistant to SCH-C and other anti-CCR5 compounds
- All resistant viral envelopes tested remained R5-tropic
  - No emergence of X4-tropic viruses
- Sequence analysis of serial envelopes has revealed 23 amino-acid differences between passage-24 and parental viruses
  - 13 in gp120 and 10 in gp41

Chen et al., 2004 11th Retro. Conf. & OI
BMS-043 Blocks HIV Entry by Disrupting gp120-CD4 Interaction

- BMS-043 blocks gp120-CD4 interaction
- CCR5 or CXCR4 Inhibitors
- T-20 or T-1249
- V3 Loop
Small-Molecule HIV-1 Attachment Inhibitor, BMS-488043
Single Oral Doses in Healthy Subjects

- Ascending single-dose study with 6 groups of subjects
  - 6 active and 2 placebo per group
- Two (2) single doses:
  - 200-, 400-, 800-, 1200-, 1800-, or 2400-mg capsules
  - Second dose as solution (200-mg)
  - After ritonavir pretreatment (400-mg)
  - After a high fat meal (800- and 1800-mg)
Small-Molecule HIV-1 Attachment Inhibitor, BMS-488043
Single Oral Doses in Healthy Subjects

- Median $T_{\text{max}}$ was 1 to 2 hours
- Mean $C_{\text{max}}$ was 662 to 1790 ng/mL for 200- to 2400-mg groups
- $C_{\text{max}}$ and AUC were dose related
- Ritonavir pretreatment increased 043 exposure by 43%
- Solution increased exposure 3-fold
- Administration with food showed 3- to 5-fold increased exposure

Hanna et al., 2004 11th Retro. Conf. & OI
Small-Molecule HIV-1 Attachment Inhibitor, BMS-488043
Multiple Oral Doses in Healthy Subjects

• Four (4) groups of subjects
• 400-, 800-, 1200-, or 1800-mg doses every 12 hours for 14 days
• Either a high fat meal \((n = 5 \text{ per group})\) or a light meal \((n = 5 \text{ per group})\)
• Subjects were randomized with 4 active/1 placebo per group/meal type
## Small-Molecule HIV-1 Attachment Inhibitor, BMS-488043
### Multiple Oral Doses in Healthy Subjects

<table>
<thead>
<tr>
<th>Day</th>
<th>Dose (mg)</th>
<th>Exposure (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>400</td>
<td>7136</td>
</tr>
<tr>
<td></td>
<td>1800</td>
<td>34,986</td>
</tr>
</tbody>
</table>

- **Median T<sub>max</sub>**: 3 hours, 4 hours
- **Mean C<sub>max</sub>**: 2494 ng/mL, 7136 ng/mL
- **AUC<sub>0-12</sub>**: 10,643 ng·h/mL, 34,986 ng·h/mL
- **C<sub>min</sub>**: 139 ng/mL, 745 ng/mL

Accumulation indices from 1.1 to 1.6
Exposures were higher with high fat meal, dose proportional from 400 to 1200 mg, but exposure did not significantly increase above these doses

Hanna et al., 2004 11th Retro. Conf. & OI
BMS-043 in HIV Infected Subjects

- No medical indication for antiretroviral therapy
  - Naïve or off therapy for greater than 16 weeks
- CD4 cell count of greater than 250 cells/mL
- HIV RNA 5-500K copies/mL
- Two groups of 15 HIV-1 infected adults (12 active/three placebo per group)
- 800 or 1800 mg doses using 200 mg capsules of BMS-488043 or placebo every 12 hours for seven days with a high-fat meal
BMS-043 in HIV Infected Subjects

- Mean age 39 - 41 years
- Mean HIV RNA 16,000 - 58,000 copies/ml
- Mean CD4 count 372 - 413/mL
BMS-043 in HIV Infected Subjects

- No serious adverse events reported
- 24 mild adverse events for all the patients
- 3 moderate adverse events (fatigue, abscesses, diarrhea)
- No grade 3 or 4 lab abnormalities or adverse events
- BMS-488043 was safe and well tolerated for 8 days.
Resistance to BMS-043

- Isolates were passaged in vitro in the presence of increasing concentrations of 043
- Genotypic analysis of the envelope gene
- Substitutions were predominantly within gp120
  - V68A, M426L, M434I, S440R, and M475I
- M426L or M475I near the CD4 contact points conferred high levels of resistance
- Did not affect gp120/CD4 interactions
- W427V eliminated CD4/gp120 binding and eliminated the binding of 043 to gp120
- S375W (CD4-phe43 binding cavity) stabilized gp120 binding to CD4 and diminished binding to 043

Lin et al., 2004 11th Retro. Conf. & OI
Reversible Changes in Dominant R5:X4 Species After UK-427,857

- Receptor tropism at baseline, days 11 and 40
- Viable env clones from each time-point were sequenced
- CCR5 receptor binding was measured using an ex vivo receptor saturation assay
- Single patient experienced no drop in viral load
- PK and CCR5 receptor saturation was within the normal range of responders
- Dual tropic phenotype with a predominance of R5 variants at baseline suppressed during treatment and became dominant after treatment

Westby et al., 2004 11th Retro. Conf. & OI
Ono Here Comes GW873140

CCR5 Receptor
Ono Here Comes GW873140
-- In Healthy Subjects

- Double blind, randomized, placebo-controlled single and multiple oral dose escalation study
- 70 fasted subjects (57 males, 13 females)
- Single dose escalation
  - 3 cohorts of 10 subjects (8 active / 2 placebo) received doses of 50, 200, 400, 800, 1200 mg, or 400 mg + standard breakfast in an alternating panel design
- Multiple dose escalation
  - 4 cohorts (8 active / 2 placebo) received doses of 200, 400, 600, or 800 mg as a single dose on day 1 and then twice daily for 7 days
- CCR5 occupancy was evaluated using flow cytometric analysis
Ono Here Comes GW873140
-- In Healthy Subjects

- GW873140 was well tolerated with no serious adverse events and no grade 3 or 4 adverse events
- Mild to moderate side effects included abdominal cramping, nausea, and diarrhea
- Median AUC and $C_{\text{max}}$ ranged from 127 ng*h/mL and 24 ng/mL at 200 mg twice daily to 329 ng*h/mL and 100 ng/mL at 800 mg BID
- Food increased the AUC and $C_{\text{max}}$ by a mean of 1.7- and 2.2-fold
- CCR5 occupancy was $>97\%$ at 2 and 12 hours after multiple dosing
A Solution to the R5:X4 Problem?

- AMD887 blocks CCR5 but not CXCR4 (SI virus)
- AMD070 blocks CXCR4 but not CCR5 (NSI virus)
- Each individually blocks the respective tropic virus
- In combination, these agents prevent replication of mono- and dual tropic HIV isolates

Schols et al., 2004 11th Retro. Conf. & OI
Reversible CCR5 CXCR4 Selection After Receptor Antagonist Use

Treatment with CXCR4 Antagonist

Treatment with CCR5 Antagonist
Use of Both CCR5 and CXCR4 Receptor Antagonists Blocks Escape

Treatment with CXCR4 (AMD877) Antagonist and treatment with CCR5 (AMD070) Antagonist
What’s A Physician To Do?

• Smile again
• Be happy mon
• Two entirely new groups of entry inhibitors (gp120-CD4 and gp120-Chemokine Receptor) are in the clinic
• Likely to be rapidly developed given need and newness of mechanisms
• We now have a potential “Quad” regimen of entry inhibitors!
Compartmental Ablation for HIV

Antiretroviral Therapy

Supportive Care

Ablation Therapy

CD4+ Cells

Time (Months)

0 6 12 48

Total

Naive
Regimen A

5

28

6 Months

Immune Recovery
Regimen B

5
35
70

Immune Recovery