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Content

• The past

• The present

• The future
HIV therapy: from saving lives to chronic management

The first ARV, AZT, is approved, for the treatment of HIV\(^1\)

The introduction of third agents marked the beginning of the era of HAART\(^2\)

Single-tablet triple regimen (EFV/FTC/TDF) approved\(^3\)

First INI, raltegravir approved\(^2,4\)

Launch of dolutegravir, the first ARV with head-to-head data in multiple patient populations at approval\(^5\)

First 2DR approved\(^6\)

Summary efficacy and safety of PI/r +3TC or TDF

N = 1635 patients
Why DTG – based 2DR?

• Avoid boosting agents (< DDI) when possible

• Demonstrated superior efficacy vs 3 ART classes: NNRTI, PI and INSTI

• DTG – high genetic barrier: high IQ - extremely low rates of resistance development in Phase III clinical trials

• To be combined with other unboosted drugs – ideally to match PK profile to avoid mono-therapy if drug doses are delayed
Matched PK profiles

Steady-state DTG or intracellular 3TC-TP concentration–time profiles

- DTG 50 mg QD
- Intracellular 3TC-TP 300 mg QD

In vitro DTG PA-IC\textsubscript{90} (0.064 µg/mL)

In vitro RPV PA-IC\textsubscript{90} (12.5 ng/mL)


3TC-TP, lamivudine triphosphate.
Available data

3TC + DTG
- Naïve
  - Paddle
  - ACTG5353
  - Gemini 1 and 2
- Switch
  - ASPIRE
  - Real world experience/cohorts

RPV + DTG
- Naïve
  - Not indicated
- Switch
  - Sward 1 and 2
GEMINI-1 and -2: Phase III Study Design

Identically designed, randomised, double-blind, parallel-group, multicentre, non-inferiority studies

- ART-naive adults
- ≤10 days of prior ART
- VL 1,000–500,000 c/mL
- No evidence of pre-existing resistance based on presence of any major RAM

Day 1

Week 48

Week 96

Week 148

Screening

Double-blind phase

Open-label phase

• ART-naive adults
• ≤10 days of prior ART
• VL 1,000–500,000 c/mL
• No evidence of pre-existing resistance based on presence of any major RAM

Primary endpoint at Week 48: subjects with HIV-1 RNA <50 c/mL (ITT-E Snapshot)*

Countries
- Argentina
- Canada
- Italy
- Netherlands
- Portugal
- South Africa
- Taiwan
- Australia
- France
- Republic of Korea
- Peru
- Romania
- Spain
- United Kingdom
- Belgium
- Germany
- Mexico
- Poland
- Russian Federation
- Switzerland
- United States


* ≤10% non-inferiority margin for individual studies

Baseline stratification factors: plasma HIV-1 RNA (≤100,000 c/mL vs >100,000 c/mL) CD4+ cell count (≤200 cells/mm³ vs >200 cells/mm³)

Exclusion criteria included severe hepatic impairment or unstable liver disease; evidence of hepatitis B virus infection at screening; anticipated need for hepatitis C virus therapy in the first 48 weeks; creatinine clearance <50 mL/min.
DTG + 3TC was non-inferior to DTG + TDF/FTC in the proportion of patients with <50 c/mL HIV-1 RNA at Week 48 in pooled Snapshot data using either the ITT-E or PP populations.

- Data pooled from both GEMINI-1 and -2 studies
- PP population consisted of subjects in the ITT-E population except those with protocol violations that could affect assessment of antiviral activity; *Based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline stratification factors: plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm^3). † PP, per protocol

GEMINI 1 and 2: confirmed virologic withdrawals through wk 48

- Low rates of virologic withdrawals were observed by Week 48

<table>
<thead>
<tr>
<th></th>
<th>DTG + 3TC (N=716)</th>
<th>DTG + TDF/FTC (N=717)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVW, n (%)</td>
<td>6 (&lt;1)</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>Virologic rebound, n (%)</td>
<td>6 (&lt;1)</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>Treatment-emergent resistance, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

No treatment-emergent INI or NRTI mutations were observed among subjects who met CVW criteria

Other results: subpopulations, baseline VL, baseline CD4 (difference at snapshot analysis but not lack of efficacy of 2DR), target not detected, viral load decay rate, no differences in AEs, renal markers, bone markers, lipids...

### What else would we want to know?

#### Efficacy and safety
- Long-term data?
- Use in broad patient populations?
- Real-world data?
- Direct comparison vs FTC/TAF-based regimens?

#### Resistance?
- Long term rates of resistance?
- Impact of mutations on virological response?
- Implications for treatment forgiveness?

#### Data in special populations?
- Pregnancy?
- Hepatitis B?
- T&T?

#### Impact on viral reservoir and immune activation?
- Sanctuaries

ETC...
What else would we want to know?

**Efficacy and safety**
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- Sanctuaries

ETC...
ACTG5353

- Phase 2, single-arm, pilot study of DTG OD (50 mg) plus 3TC (300 mg) in treatment-naive participants with HIV-1 RNA ≥1000 and <500 000 copies/mL
- Exclusion criteria included active hepatitis B or major protease, reverse transcriptase, or integrase resistance. The primary efficacy measure was the proportion with HIV-1 RNA <50 copies/mL (FDA Snapshot) at week 24
- Virologic failure (VF) was confirmed HIV-1 RNA >400 copies/mL at week 16/20 or >200 copies/mL at or after week 24
- DTG levels and drug resistance testing were performed at VF
HIV-1 RNA, DTG plasma concentration, and genotyping results for virologic failures and Snapshot nonsuccesses

- Open circles represent HIV-1 RNA results that are less than the lower limit of quantification.
- Open diamonds represent drug level below the in vitro inhibitory concentration for 90% inhibition (IC90) (64 ng/mL).
- Participants 3, 4, and 5 had at least 1 time point with undetectable plasma DTG. Resistance mutations are shown at the time points tested, with “None” representing no mutation detected.
- Vertical dashed line represents discontinuation of study treatment.
- Horizontal dashed line represents HIV-1 RNA 50 copies/mL.
## What else would we want to know?

### Efficacy and safety
- Long-term data?
- Use in broad patient populations?
- Real-world data?
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### Resistance?
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- Pregnancy?
- Hepatitis B?
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### Impact on viral reservoir and immune activation?
- Sanctuaries

ETC...
### DTG/3TC: ACTG5353 & ASPIRE

<table>
<thead>
<tr>
<th>Parent study</th>
<th>Study week</th>
<th>ART regimen</th>
<th>Last missed doses</th>
<th>Genital HIV RNA (copies/ml)</th>
<th>Plasma HIV RNA* (copies/ml)</th>
<th>CMV DNA (copies/ml)</th>
<th>HSV DNA (copies/ml)</th>
<th>Gonorrhea RNA</th>
<th>Chlamydia RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPIRE #1</td>
<td>48</td>
<td>RPV/TDF/FTC</td>
<td>1-2 weeks</td>
<td>42</td>
<td>179</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
<tr>
<td>ASPIRE #2**</td>
<td>36</td>
<td>DTG+3TC</td>
<td>&gt; 3 months</td>
<td>488</td>
<td>&lt;20</td>
<td>314607</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>DTG+3TC</td>
<td>Never</td>
<td>79</td>
<td>31</td>
<td>86090</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
<tr>
<td>A5353</td>
<td>24</td>
<td>DTG+3TC</td>
<td>Never</td>
<td>48</td>
<td>&lt;40</td>
<td>NA***</td>
<td>NA***</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
</tbody>
</table>

**Legend:** RPV: Rilpivirine, TDF: Tenofovir, FTC: emtricitabine, DTG: Dolutegravir, 3TC: Lamivudine. NA = not available. *Plasma HIV RNA at the same time of genital HIV RNA shedding. **ASPIRE participant #2 had detectable HIV RNA at two consecutive time-points. ***not enough semen sample to run these additional tests.

3/45 had HIV RNA > 40 in SP

1/20 (5% [95%CI: 0.1%, 25%]) in the ASPIRE threedrug ART arm.
1/18 (5.6% [0.1%, 27%]) in the ASPIRE DTG+3TC arm.
1/13 (7.7% [0.2%, 36%]) in A5353 (DTG+3TC).

No women had detectable genital HIV RNA.

2-20% on suppressive 3DR have detectable genital HIV-RNA
Conclusions

- Genital HIV RNA shedding was comparable between virologically suppressed individuals receiving initial or maintenance DTG+3TC and those on three-drug ART.
- These results suggest that DTG+3TC may confer similar transmission prevention benefits as triple therapy.
- It is unknown if HIV RNA in genital secretions represent replication competent or transmissible virus.

HIV genotyping and urine PCR for gonorrhea and chlamydia were performed if genital HIV RNA was detected.
Do sanctuary drug concentrations matter?
SWORD 1 and 2: DTG + RPV

Identically designed, randomised, multicentre, open-label, parallel-group, noninferiority studies

Inclusion criteria
- On stable CAR ≥6 months before screening
- 1st or 2nd ART with no change in prior regimen due to VF
- Confirmed HIV-1 RNA <50 c/mL for ≥6 months at screening
- HBV negative

Primary endpoint at 48 weeks: subjects with VL <50 c/mL (ITT-E snapshot)*

*~8% non-inferiority margin for pooled data; ~10% non-inferiority margin for individual studies.

CAR, current antiretroviral regimen; VF, virologic failure; VL, viral load.

SWORD 1 and 2: DTG + RPV was efficacious in the early-switch group through 148 weeks

• Through 148 weeks of treatment, DTG + RPV maintained virological suppression in 84% of patients in the early-switch group

• Virological efficacy in the late-switch group at Week 148 was similar to that of the early-switch group at wk 100

Injectable CAB/RPV – Phase III results

**ATLAS**

**Screening Phase**
- N=705
- PI, NNRTI-, or INSTI-based regimen with 2 NRTI backbone

**Induction Phase**
- CAB LA (400 mg) + RPV LA (600 mg)
- IM monthly n=278

**Maintenance Phase**
- CAB LA (400 mg) + RPV LA (600 mg)
- Oral CAB + RPV n=308

**Extension Phase**
- Extension Phase or transition to the ATLAS-2M study

**Primary Endpoint**
- Day 1 Baseline
- Study Week 4
- Study Week 48
- Study Week 52
- Week 96

**FLAIR**

**Screening Phase**
- N=809
- ART-naive
- HIV-1 RNA ≥1000
- Any CD4 count
- HBsAg negative
- NNRTI RAMs excluded

**Induction Phase**
- N=629
- DTG/ABC/3TC single-tablet regimen for 20 weeks

**Maintenance Phase**
- Oral CAB + RPV n=283

**Extension Phase**
- CAB LA (400 mg) + RPV LA (600 mg)
- IM monthly n=278

**Primary Endpoint**
- Confirm HIV-1 RNA <50 copies/mL

Swindells et al. CROI 2019, abstract 139; Orkin et al. CROI 2019, abstract 140LB
### ATLAS and FLAIR confirmed virologic failures: CAB LA + RPV LA

<table>
<thead>
<tr>
<th>Sex, Country, HIV-1 Subtype</th>
<th>Previous CAR</th>
<th>SVF Timepoint</th>
<th>Viral Load at SVF/CVF (c/mL)</th>
<th>SVF Timepoint RAMs (HIV-1 RNA)</th>
<th>Drug Sensitivity at SVF† (Fold Change)</th>
<th>Baseline RAMs (PBMC/HIV-1 DNA; Day 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F, Russia, A/A1</td>
<td>3TC, AZT, LPV/r</td>
<td>Week 8</td>
<td>79,166 / 25,745</td>
<td>E138A</td>
<td>RPV (2.4) CAB (0.8) DTG (0.9)</td>
<td>E138E/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>L74I</td>
<td></td>
<td>L74I</td>
</tr>
<tr>
<td>F, France, AG</td>
<td>3TC, AZT, NVP to 3TC, ABC, NVP</td>
<td>Week 12</td>
<td>695 / 258</td>
<td>V108I E138K</td>
<td>RPV (3.7) CAB (1.2) DTG (1.0)</td>
<td>V108V/I E138K</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>None</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>M, Russia, A/A1</td>
<td>FTC, RAL, TDF to ABC, EFV, 3TC</td>
<td>Week 20</td>
<td>544 / 1841</td>
<td>E138E/K N155H L74I</td>
<td>RPV (6.5) CAB (2.7) DTG (1.2)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>L74I</td>
</tr>
</tbody>
</table>

#### Baseline RAMs (Baseline Load (Baseline))

<table>
<thead>
<tr>
<th>Sex, Country, HIV-1 Subtype, Virologic Load (Baseline)</th>
<th>Baseline RAMs (HIV-1 RNA)</th>
<th>SVF Timepoint</th>
<th>Viral Load at SVF/CVF (c/mL)</th>
<th>SVF Timepoint RAMs (HIV-1 RNA)</th>
<th>Drug Sensitivity at SVF† (Fold Change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F, Russia, A1, 54K</td>
<td>None L74I</td>
<td>Week 20</td>
<td>373 / 456</td>
<td>E138E/A K/T</td>
<td>RPV (7.1) CAB (5.2) DTG (1.0)</td>
</tr>
<tr>
<td>M, Russia, A1, 23K</td>
<td>None L74I</td>
<td>Week 28</td>
<td>287 / 299</td>
<td>K101E</td>
<td>RPV (2.6) CAB (6.7) DTG (2.2)</td>
</tr>
<tr>
<td>F, Russia, A1, 20K</td>
<td>None L74I</td>
<td>Week 48</td>
<td>488 / 440</td>
<td>E138K</td>
<td>RPV (1.0) CAB (9.4) DTG (1.1)</td>
</tr>
</tbody>
</table>
MK-8591 + doravirine and 3TC in participants infected with HIV: DRIVE2Simplify

• Participants will be treated OD with MK-8591, 100 mg DOR, 300 mg 3TC, and placebo to MK-1439A for a minimum of 24 weeks

• Between week 24 through week 52, 3TC and placebo to MK-1439A may be discontinued

• Around Week 60, participants may be switched to a selected open label dose of MK-8591 and DOR 100 mg OD and continue treatment until Week 120
New combinations/drugs: candidates for 2DR?

• DOR + DTG
• GS-CA1 + ?
• Other LA ARVs
Conclusions

• Extensive experience and data on 3DR but 2DR might be the future
• Drug characteristics (genetic barrier, IQ, PK forgiveness, etc.)
• Long acting, injectables, implants etc. in development – cost will matter...
• No drug is magic...

THANK YOU