Dolutegravir in the treatment of HIV/AIDS naïve patients

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Global Medical Director, ViiV Healthcare
CONFLICT OF INTERESTS

I am a full time employee of ViiV Healthcare.

This event is sponsored by GSK/ViiV, in the interest of advancing the scientific knowledge of healthcare professionals.

GSK/ViiV does not approve of or recommend the use of medicines in any way other than that stated in the approved package inserts.
AGENDA

• Basic & General HIV Therapy Recommendations.

• What advantages INI-family may offers?

• DTG. Scientific data in support for a long term success.
  • Real world data
### Comparison of Current International Guidelines for Treatment-Naive Pts

<table>
<thead>
<tr>
<th>Regimen</th>
<th>DHHS</th>
<th>EACS</th>
<th>BHIVA</th>
<th>IAS-USA</th>
<th>GeSIDA</th>
<th>Portugal</th>
</tr>
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<tbody>
<tr>
<td>DTG/3TC/ABC*</td>
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<td>DTG + FTC/TDF</td>
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<td>EVG/COBI/FTC/TDF†</td>
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<td>EVG/COBI/FTC/TAF‡</td>
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<td>RAL + FTC/TDF</td>
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<td>ATV/RTV + FTC/TDF</td>
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<td>DRV/RTV + FTC/TDF</td>
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<td>EFV/FTC/TDF</td>
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<tr>
<td>RPV/FTC/TDF§</td>
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</table>

*Only if HLA-B*5701 negative.
†Only if CrCl ≥ 70 mL/min.
‡Only if CrCl ≥ 30 mL/min.
§Only if baseline HIV-1 RNA < 100,000 copies/mL and CD4+ cell count > 200 cells/mm³.

- **Recommended**
- **Alternative**
- **Not included**

Adapted from references 1-6
MEAN EFFICACY OF INITIAL REGIMEN CONTINUES TO RISE FROM 77% (2005–2010) TO TODAY’S 48W RESULTS

Patients with plasma HIV-1 RNA <50 copies/mL at week 48 (%) 

3TC = lamivudine; ABC = abacavir; DTG = dolutegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; RAL = raltegravir; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate

Adapted from references 7-15

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**UCHCC: UNC CFAR HIV Clinical Cohort**

**Persistence of Initial ART**

**Time on Initial ART, UCHCC 1996-2014**

**INITIAL ANTIRETROVIRAL THERAPY**
- **INSTI** (N=175)
- **NNRTI** (N=547)
- **bPI** (N=340): LPV/r, DRV/r, ATV/r
- **Other** (N=459): incl. unboosted and other bPI
- **NRTI only** (N=252)

**INSTI** hazard ratio: **0,49** (95%CI: 0,35-0,69) for **DC** and **0,70** (95% CI: 0,46-1,06) for **VF** compared to **NNRTI**.

Adapted from reference 16
Domain organisation of retroviral integrases

- **HIV-1**
  - NED: 1, 20
  - NTD: 47, 59
  - CCD: 202, 223
  - CTD: 270, 288

- **RSV**
  - NED: 1, 13
  - NTD: 44, 58
  - CCD: 213, 222
  - CTD: 268, 286

- **MLV**
  - NED: 1, 105
  - NTD: 45, 105
  - CCD: 287, 329
  - CTD: 381, 408

- **PFV**
  - NED: 1, 20
  - NTD: 51, 102
  - CCD: 271, 321
  - CTD: 374, 392

Adapted from reference 17
HIV PROTEOMICS

**RETRORTRANSCRIPTASE**
- Error prone: $10^5$ - $10^6$ pairs
- Inhibition of γ-DNA mitochondrial polymerase

**PROTEASE**
- Functional and structural plasticity
- High homology to signal proteins involved in lipid metabolism: CRABP-1, LRP

**INTEGRASE**
- Unique to Retroviruses
- Highly efficient enzyme; viral DNA strand transfer

Adapted from references 18-20
MOLECULAR BIOLOGY OF INSTI
MOLECULAR BIOLOGY OF INSTI

- Magnesium and Aluminium containing antiacids.
- Calcium and Iron supplements

Taken separately: minimum 2 hr after or 6 hr before

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Adapted from references 21 and 22
It should be noted that there are inherent limitations of comparing data across trials. Head-to-head studies with DTG have not been conducted. Doses may differ from approved dose.
More Rapid Viral Suppression With INSTI-Based ART vs EFV-Based ART

STARTMRK

Study 102

SINGLE

Adapted from references 11, 13, 15

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VIROLOGIC RESPONSE AT WEEK 48

![Graph showing virologic response at week 48 with proportions of HIV-1 RNA <50 c/mL for different treatment groups.]

- **DTG**: 90%
- **DRV/r**: 83%

Results confirmed in per protocol analysis: 91% DTG versus 84% DRV/r (difference [95% CI]: 7.4% [−13.3])

1 Adjusted difference (DTG - DRV/r) based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline HIV-1 RNA and background NRTI therapy; †plus 2 NRTIs

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VIROLOGIC RESPONSE AT WEEK 48

Weeks

Proportion with HIV-1 RNA <50 c/mL

- Integrase; life cycle
- Active in Monocyte/macrophages.
- Deeper phase I VL decay.

Results confirmed in per protocol analysis: 91% DTG versus 84% DRV/r (difference [95% CI]: 7.4% [-13.3])

*Adjusted difference (DTG - DRV/r) based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline HIV-1 RNA and background NRTI therapy;
†plus 2 NRTIs

Material de autoria e propriedade GSK, a reprodução deste é proibida sem o consentimento da empresa.

Adapted from references 9 and 24-27
VIROLOGIC RESPONSE AT WEEK 48

- MDR and Dx late in Pregnancy
- Surgical urgency
- Faster CD4/CD8 normalization in VL<50c/mL w8.
- VL<50c/mL W4: 70% of then 80% supressed by w96.

Results confirmed in per protocol analysis: 91% DTG versus 84% DRV/r (difference [95% CI]: 7.4% [−13.3])

*Adjusted difference (DTG - DRV/r) based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline HIV-1 RNA and background NRTI therapy;
†plus 2 NRTIs

Adapted from references 9 and 24-29
What are the desired characteristics of an IDEAL cART regimen?

✓ Highly Efficacious
✓ Safe and Well Tolerated
✓ High Genetic Barrier to Resistance
✓ Convenience
✓ DDI- no/few
DOLUTEGRAVIR-BASED REGIMENS: SUPERIOR EFFICACY IN 4 COMPARATIVE STUDIES

Superior efficacy vs 3 ARV classes: NNRTI, boosted PI and INI

**Treatment-naïve adults**

**Superior efficacy vs EFV/TDF/FTC**
- at weeks 48, 96 and 144
- SINGLE:
  - DTG + ABC/3TC QD vs EFV/TDF/FTC QD
  - (N=833)

**Superior efficacy vs darunavir/r**
- at weeks 48 and 96
- FLAMINGO:
  - DTG 50 mg + 2 NRTIs QD vs DRV/r 800mg/100mg + 2 NRTIs QD
  - (N=484)

**Comparable efficacy vs raltegravir**
- at weeks 48 and 96
- SPRING-2:
  - DTG 50 mg QD + 2 NRTIs vs RAL 400 mg BID + 2 NRTIs
  - (N: DTG=411 / RAL=411)

**Superior efficacy vs ATV/r**
- at week 48 in ARIA
- DTG / ABC/3TC FDC\(^1\) QD vs ATV/r + TDF/FTC FDC
  - (N=495)

**Treatment-experienced adults**

**Superior efficacy vs raltegravir**
- up to week 48
- SAILING:
  - DTG 50 mg QD + BR vs RAL 400 mg BID + BR
  - (N=715)

**Sustained efficacy**
- up to week 48
- VIKING-3:
  - DTG 50 mg BID + OBR
  - (N=183)

**Maintained efficacy**
- vs continuation of current ARV regimen
- up to week 24
- STRIVING:
  - DTG/ABC/3TC QD vs cART
  - (N=551)

**Heavily treatment-experienced adults**

**Superior response in high VL (>5 logHIV RNA): 78 vs 63%**
CHALLENGING (BUT FREQUENT) CLINICAL SCENARIOS

- Late presenter (or advance, with/out AIDS)
- Young MSM on Chem SEX (weekend; condomless behaviour)
- PHI.
- Confirmed (or perceived) poor ART adherence.
- Women on childbearing age (or not on birth control compliance) or looking for pregnancy.
- HIV patient with a long history of ARV intolerance or toxicity.
- HCV or HBV coinfection with liver fibrosis.
- Ageing patient harbouring multiple comorbidities. (or at high risk to developed).
Substantial proportion of patients are Late Presenter (CD4 <350 c/mm³)
What exactly is a Late Presenter?

HR: 0.43

68%, CD4 >500 c/mm³

Adapted from reference 44
LPV HAS SHOWN TO BE INFERIOR TO EFV PARTICULARLY IN ADVANCED HIV PTS

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Adapted from references 45 and 46
LPV HAS SHOWN TO BE INFERIOR TO EFV PARTICULARLY IN ADVANCED HIV PTS

Adapted from references 45 and 46

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### Virologic Response by Baseline Viral Load and Dual NRTI Therapy at Week 96

<table>
<thead>
<tr>
<th>Baseline HIV-1 RNA</th>
<th>ABC/3TC</th>
<th>TDF/FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤100,000 c/mL</td>
<td></td>
<td></td>
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<tr>
<td>&gt;100,000 c/mL</td>
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</tr>
</tbody>
</table>

- **Overall**: N=484, n=362, n=122
- **≤100,000 c/mL**: 80% (n=242), 73% (n=159)
- **>100,000 c/mL**: 82% (n=242), 52% (n=159)
- **Background NRTI**: 82% (n=325), 75% (n=325)

**Proportion with HIV-1 RNA <50 c/mL (%)**

<table>
<thead>
<tr>
<th>DTG 50 mg QD (n=242)</th>
<th>DRV/r 800/100 mg QD (n=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>68%</td>
<td>73%</td>
</tr>
<tr>
<td>82%</td>
<td>52%</td>
</tr>
<tr>
<td>79%</td>
<td>75%</td>
</tr>
<tr>
<td>82%</td>
<td>79%</td>
</tr>
<tr>
<td>64%</td>
<td>79%</td>
</tr>
</tbody>
</table>

Adapted from reference 31

Material de autoria e propriedade GSK, a reprodução deste é proibida sem o consentimento da empresa.
# 96-WEEK SNAPSHOT RESPONSE (HIV-1 RNA <50 C/ML) IN SUBJECTS WITH HIGH BL VL AND LOW BL CD4

<table>
<thead>
<tr>
<th>HIV-1 RNA &lt;50 c/mL (Snapshot), n/N (%)</th>
<th>SPRING-2</th>
<th>SINGLE</th>
<th>FLAMINGO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTG</td>
<td>RAL</td>
<td>DTG</td>
</tr>
<tr>
<td>Overall</td>
<td>332/411</td>
<td>314/411</td>
<td>332/414</td>
</tr>
<tr>
<td></td>
<td>(81%)</td>
<td>(76%)</td>
<td>(80%)</td>
</tr>
</tbody>
</table>

**Individuals with high baseline VL (>100,000 c/mL) by background regimen**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n/N (%)</th>
<th>n/N (%)</th>
<th>n/N (%)</th>
<th>n/N (%)</th>
<th>n/N (%)</th>
<th>n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC/3TC</td>
<td>27/37 (73%)</td>
<td>26/39 (67%)</td>
<td>95/134 (71%)</td>
<td>- (--)</td>
<td>11/13 (85%)</td>
<td>7/12 (58%)</td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>62/77 (81%)</td>
<td>47/77 (61%)</td>
<td>- (--)</td>
<td>94/131 (72%)</td>
<td>39/48 (81%)</td>
<td>25/49 (51%)</td>
</tr>
</tbody>
</table>

**Individuals with low baseline CD4**

<table>
<thead>
<tr>
<th>CD4 Count</th>
<th>n/N (%)</th>
<th>n/N (%)</th>
<th>n/N (%)</th>
<th>n/N (%)</th>
<th>n/N (%)</th>
<th>n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200 cells/mm³</td>
<td>39/55 (71%)</td>
<td>28/50 (56%)</td>
<td>39/57 (68%)</td>
<td>45/62 (73%)</td>
<td>18/23 (78%)</td>
<td>14/24 (58%)</td>
</tr>
<tr>
<td>200 to &lt;350 cells/mm³</td>
<td>116/144 (81%)</td>
<td>103/139 (74%)</td>
<td>135/163 (83%)</td>
<td>113/159 (71%)</td>
<td>60/73 (82%)</td>
<td>36/51 (71%)</td>
</tr>
</tbody>
</table>

Adapted from reference 48
Adjusted mean change from baseline
CD4+ cell count (cells/mm$^3$)

DTG+ABC/3TC
267 cells/mm$^3$

EFV/TDF/FTC
208 cells/mm$^3$

Week 48 difference in response (95% CI):
59 (33 to 84); P<0.001

DTG 50 mg + ABC/3TC FDC QD
EFV/TDF/FTC QD

MEAN CHANGE IN CD4+ CELL COUNT
AT WEEK 48, WEEK 96 AND WEEK 144

At Week 96, mean change from baseline was +325 cells/mm$^3$ versus +281 cells/mm$^3$; p=0.004)

At Week 144, mean change from baseline was +378 cells/mm$^3$ versus +332 cells/mm$^3$; p=0.003)

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STUDY OF THE INTERACTION BETWEEN DTG AND RIFAMPIN IN HEALTHY SUBJECTS

Co-administration of DTG 50 mg BID with rifampin resulted in similar DTG concentrations as with DTG 50 mg QD alone

<table>
<thead>
<tr>
<th>Regimen</th>
<th>C_{max} (µg/mL)</th>
<th>AUC_{0–24} (µg·h/mL)</th>
<th>C_{t} (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG 50 mg QD vs DTG 50 mg BID + rifampin 600 mg QD</td>
<td>1.18 (1.03–1.37)</td>
<td>1.33 (1.15–1.53)</td>
<td>1.22 (1.01–1.48)</td>
</tr>
</tbody>
</table>

Values shown are GLS mean ratio (90% CI); For BID dosing, simulations of the concentrations after a second dose are provided.

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Adapted from reference 49
CHALLENGING (BUT FREQUENT) CLINICAL SCENARIOS

• Late presenter (or advance, with/out AIDS)
• Young MSM on Chem SEX (weekend; condomless behaviour)
• PHI.
  • Confirmed (or perceived) poor ART adherence.
  • Women on childbearing age (or not on birth control compliance) or looking for pregnancy.
• HIV patient with a long history of ARV intolerance or toxicity.
• HCV or HBV coinfection with liver fibrosis.
• Ageing patient harbouring multiple comorbidities. (or at high risk to developed).
CLINICAL CASE

Primary HIV Infection.

- 32yr MSM, history of syphilis and anal lymfogranuloma venereum
- ER after 8 days with headache, photophobia, fever, sore throat and morbilliform rash. Tender lymph nodes in neck, axilla; exudative pharyngitis.
- ELISA HIV neg; PCR: 3.755.000 cRNA/mL.

Pharyn swab culture: *N gonorrhea*; Tx: CTX 250 mg IM

Source: Personal File

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Plasma protein binding: ≥99.3%

A Phase IIIb study assessed the distribution of DTG in CSF

DTG concentrations observed in CSF at both Week 2 and Week 16 exceeded the in-vitro IC\textsubscript{50} against wild-type viruses (0.2 ng/mL) for all subjects, suggesting that DTG was able to achieve therapeutic concentrations in the CSF.

The estimated DTG Free concentrations in Seminal plasma at weeks 4 and 24 exceed 170-fold and 280-fold the \textit{in vitro} unbound EC\textsubscript{50} for wild type HIV-1 (0.21 ng/mL).

Rectal tissue concentration is 2 fold higher than PA-IC90. Ileum terminal concentrations slightly lower than plasma but >IC-90.

No adjustment in patients with hepatic (up to Child B) or renal insufficiency (CreaCl>30 mL/min).
HIV RNA decline faster with MegaHAART

HAART: TDF + FTC + EFV
MegaHAART: Intensified with RAL and MVC for the first 24 weeks

Median time to HIV RNA < 50 copies/ml
HAART 83 days vs. megaHAART 55 days (p = 0.04)

Seminal plasma: Time to HIV RNA < 50 copies/ml
HAART 24 days vs. megaHAART 13 days (p=0.04)

Adapted from references 53 and 54
Dolutegravir. Post hoc analysis based on baseline viral load

Week 48 snapshot analysis

Baseline viral load ≤100,000 copies/mL

- **DTG + ABC/3TC**
  - 90%
- **EFV/TDF/FTC**
  - 88%
- **DTG 50 mg QD + 2 NRTIs**
  - 87%
- **DRV/r 800 mg/100 mg + 2 NRTIs**
  - 90%
- **RAL 400 mg BID + 2 NRTIs**
  - 89%

Baseline viral load >100,000 copies/mL

- **DTG + ABC/3TC**
  - 83%
- **EFV/TDF/FTC**
  - 93%
- **DTG 50 mg QD + 2 NRTIs**
  - 82%
- **RAL 400 mg BID + 2 NRTIs**
  - 75%

Proportion (%) of patients with HIV-1 RNA <50 copies/mL

Week 48 snapshot analysis

- **SINGLE†**
  - 32% of treatment-naïve patients had a baseline viral load > 100,000 copies/mL
- **FLAMINGO‡**
  - 25% of treatment-naïve patients had a baseline viral load > 100,000 copies/mL
- **SPRING-2§**
  - 28% of treatment-naïve patients had a baseline viral load > 100,000 copies/mL

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Adapted from references 9, 11, 24, 56-58
### TDR Prevalence by Class per Year

<table>
<thead>
<tr>
<th></th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>9.9%</td>
<td>5.7%</td>
<td>4.5%</td>
</tr>
<tr>
<td>NNRTI</td>
<td>13.2%</td>
<td>22.6%</td>
<td>10.2%</td>
</tr>
<tr>
<td>PI</td>
<td>4.4%</td>
<td>4.4%</td>
<td>3.4%</td>
</tr>
<tr>
<td>INI</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
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</table>
Recommendations for Initiation of ART in HIV-positive Persons with Chronic Infection without prior ART Exposure

ART is recommended in all adults with chronic HIV infection, irrespective of CD4 counts.

- ART should always be recommended irrespective of the CD4 count, but the lower the CD4 count, the greater the urgency to start ART immediately.
  - For best timing for starting ART in persons with tuberculosis and cryptococcal meningitis, see page 14 and page 85.
  - A possible exception could be elite controllers with high and stable CD4 count. Time should always be taken to prepare the person, in order to optimise compliance and adherence.
  - Genotypic resistance testing is recommended prior to initiation of ART, ideally at the time of HIV diagnosis, otherwise before initiation of ART.
  - If ART needs to be initiated before genotypic testing results are available, it is recommended to include a drug with high genetic barrier to resistance in the first-line regimen (e.g. a PI/r, PI/c or DTG). Ideally, before starting treatment, the HIV-VL level and CD4 count should be repeated to obtain a baseline to assess subsequent response.
  - Use of ART should also be recommended with any CD4 count in order to reduce sexual transmission, risk of AIDS event and mother-to-child transmission of HIV (before third trimester of pregnancy).
CHALLENGING (BUT FREQUENT) CLINICAL SCENARIOS

- Late presenter (or advance, with/out AIDS)
- Young MSM on Chem SEX (weekend; condomless behaviour)
- PHI.
- Confirmed (or perceived) poor ART adherence.
  - Women on childbearing age (or not on birth control compliance) or looking for pregnancy.
  - HIV patient with a long history of ARV intolerance or toxicity.
  - HCV or HBV coinfection with liver fibrosis.
  - Ageing patient harbouring multiple comorbidities. (or at high risk to developed).
GESIDA 2015. Adherencia

Recomendaciones

- Antes de iniciar el TAR se debe preparar al paciente, identificar y corregir las causas potenciales de adherencia incorrecta (*A-III*)
- Una vez iniciado el TAR se recomienda efectuar un control a las 2-4 semanas para comprobar la adherencia y eventualmente corregirla (*A-III*)
- La adherencia debe monitorizarse y reforzarse coincidiendo con las visitas clínicas (*A-III*)
- El control de la adherencia debe realizarse por un equipo multidisciplinar, adaptado a la disponibilidad de cada centro, que incluya a médicos, personal de enfermería, profesionales de apoyo psicológico y farmacia hospitalaria (*A-III*)
- En pacientes con cumplimiento irregular es preferible utilizar pautas basadas en IP/r (y probablemente dolutegravir) para prevenir la selección de resistencias (*A-III*). A pesar de la poca experiencia clínica disponible, los datos iniciales parecen apoyar que las pautas basadas en dolutegravir pueden ser también útiles en este tipo de pacientes (*B-III*)
# Resistance Development in INSTI HIV Naïve Clinical Trials

<table>
<thead>
<tr>
<th>INSTI</th>
<th>Trial</th>
<th>Rx Group</th>
<th>INSTI</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAL</td>
<td>STARTMRK</td>
<td>1.4%</td>
<td>1.1%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RAL (n=281)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EFV (n=282)</td>
<td>1.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVG</td>
<td>GS-US-236-102</td>
<td>2.0%</td>
<td>2.3%</td>
<td></td>
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<tr>
<td></td>
<td>EVG/c (n=348)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EFV (n=352)</td>
<td>2.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GS-US-236-102</td>
<td>1.1%</td>
<td>1.1%</td>
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</tr>
<tr>
<td></td>
<td>EVG/c (n=353)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATV/r (n=355)</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTG</td>
<td>SPRING-2</td>
<td>DTG (n=411)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>RAL (n=411)</td>
<td>0.2%</td>
<td>1.0%</td>
<td></td>
</tr>
<tr>
<td>FLAMINGO</td>
<td>DTG (n=242)</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DRV (n=242)</td>
<td>-</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>SINGLE</td>
<td>DTG (n=414)</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EFV (n=419)</td>
<td>-</td>
<td>1.2%</td>
<td></td>
</tr>
<tr>
<td>ARIA</td>
<td>DTG (n=248)</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATV/r (n=247)</td>
<td>-</td>
<td>0.4%</td>
<td></td>
</tr>
</tbody>
</table>

Material de autoria e propriedade GSK, a reprodução deste é proibida sem o consentimento da empresa.

Adapted from references 10, 11, 24, 37, 61-63
### Resistance consequences of initial InSTI-based regimen failure

<table>
<thead>
<tr>
<th>DHHS ‘preferred’ regimens</th>
<th>HIV-1 RNA &lt;50 copies/mL at week 48, %</th>
<th>Detectable resistance at virological failure*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NRTI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M184V/I</td>
</tr>
<tr>
<td>RAL, TDF/FTC*</td>
<td>86 (n=281)</td>
<td>Green</td>
</tr>
<tr>
<td>EVG/c, TDF/FTC</td>
<td>88 (n=348)</td>
<td>Red</td>
</tr>
<tr>
<td>DTG regimens</td>
<td>90 (n=242)</td>
<td>Green</td>
</tr>
</tbody>
</table>

*For patients with available baseline and post-failure genotypes

Adapted from references 24, 61, 62
# PK/PD Profile of DTG versus EVG and RAL

<table>
<thead>
<tr>
<th></th>
<th>DTG</th>
<th>RAL</th>
<th>EVG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical dose</strong></td>
<td>50 mg QD (INI-naive), 50 mg BID (INI-resistant)</td>
<td>400 mg BID</td>
<td>150 mg QD boosted (quad pill)</td>
</tr>
<tr>
<td><strong>t(_{1/2})</strong></td>
<td>~14 hours</td>
<td>~9 hours</td>
<td>~12.9 hours (boosted)</td>
</tr>
<tr>
<td><strong>PK variability</strong></td>
<td>Low-to-moderate</td>
<td>High</td>
<td>Low (with boosting)</td>
</tr>
<tr>
<td><strong>Food effect</strong></td>
<td>No food restriction</td>
<td>No food restriction, but fat content affects absorption and increases PK variability</td>
<td>Taken with food</td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>High: ≥99.3%</td>
<td>Moderate: 83%</td>
<td>High: 98–99%</td>
</tr>
<tr>
<td><strong>Metabolism and excretion</strong></td>
<td>UGT1A1 (major), CYP3A (minor), renal elimination &lt;1%</td>
<td>UGT1A1, renal elimination ~9%</td>
<td>CYP3A (major), UGT1A1/3 (minor), renal elimination 6.7%</td>
</tr>
<tr>
<td><strong>PK/PD relationship</strong></td>
<td>Yes, C(_{\text{T}})-driven efficacy</td>
<td>No</td>
<td>Yes, C(_{\text{T}})-driven efficacy</td>
</tr>
</tbody>
</table>

DTG, dolutegravir; EVG, elvitegravir; RAL, raltegravir
QD, daily; BID, twice a day; C\(_{\text{T}}\), trough concentration

Adapted from references 22, 64-68
DTG and EVG plasma concentrations up to 216 hours post-dose

**Plasma concentration** (ng/mL) vs. **Time (h)**

- **DTG** (dolutegravir)
- **EVG** (elvitegravir)
- **COBI** (cobicistat)

**Plasma concentration**

- Geometric mean
- Therapeutic target concentration

**DTG protein binding adjusted (PA) IC<sub>90</sub> (64 ng/mL)**
- **EVG protein binding adjusted (PA) IC<sub>95</sub> (45 ng/mL)**

Material de autoria e propriedade GSK, a reprodução deste é proibida sem o consentimento da empresa.

Adapted from references 69, 70
INI Dissociation from WT Integrase-DNA Complex at 37°C

DTG dissociated more slowly from a WT IN-DNA complex at 37°C compared with RAL and EVG.

DTG dissociation was eight times slower than RAL and 26 times slower than EVG.

**Table:**

<table>
<thead>
<tr>
<th>INI</th>
<th>$k_{off}$ (s$^{-1}$)</th>
<th>Dissociation $t_{1/2}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG</td>
<td>$2.7 \times 10^{-6}$</td>
<td>$7.1 \times 10^{-6}$</td>
</tr>
<tr>
<td>RAL</td>
<td>$22 \times 10^{-6}$</td>
<td>$8.8$</td>
</tr>
<tr>
<td>EVG</td>
<td>$71 \times 10^{-6}$</td>
<td>$2.7$</td>
</tr>
</tbody>
</table>

$k_{off}$, dissociation rate; $t_{1/2}$, half-life in hours

Adapted from reference 71
CHALLENGING (BUT FREQUENT) CLINICAL SCENARIOS

- Late presenter (or advance, with/out AIDS)
- Young MSM on Chem SEX (weekend; condomless behaviour)
- PHI.
- Confirmed (or perceived) poor ART adherence.
- Women on childbearing age (or not on birth control compliance) or looking for pregnancy.
- HIV patient with a long history of ARV intolerance or toxicity.
- HCV or HBV coinfection with liver fibrosis.
- Ageing patient harbouring multiple comorbidities. (or at high risk to developed).
Dolutegravir-based regimens demonstrate a good benefit-to-risk profile
- Dolutegravir-based regimens demonstrated statistically greater efficacy versus EFV/TDF/FTC at 144 weeks in the SINGLE study (P=0.010)

DOLUTEGRAVIR – OVERALL SAFETY
IN HIV NAÏVE PATIENTS

Proportion (%) of patients with AE leading to discontinuation

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>AE Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>SINGLE</td>
<td>DTG 50 mg + ABC/3TC QD (n=414)</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>EFV/TDF/FTC QD (n=419)</td>
<td>14%</td>
</tr>
<tr>
<td>SPRING-2</td>
<td>DTG 50 mg QD (n=411)</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>RAL 400 mg BID (n=411)</td>
<td>2%</td>
</tr>
<tr>
<td>FLAMINGO</td>
<td>DTG 50 mg QD (n=242)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>DRV/r 800/100 mg QD (n=242)</td>
<td>6%</td>
</tr>
</tbody>
</table>
RATES OF MOST COMMON AEs OVER 48 WEEKS (≥10%)

Any event: 89% in DTG arm versus 92% in EFV/TDF/FTC arm

Subjects experiencing AE (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>DTG + ABC/3TC QD (N=414)</th>
<th>EFV/TDF/FTC QD (N=419)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Insomnia</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9</td>
<td>35</td>
</tr>
<tr>
<td>URTI</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>14</td>
</tr>
</tbody>
</table>

Common AE (occurring ≥10%)
**DTG clinical data: psychiatric AE profiles in ART-naïve subjects**

<table>
<thead>
<tr>
<th>Cases, n (%)</th>
<th>SPRING-2†</th>
<th>FLAMINGO†</th>
<th>SINGLE†</th>
<th>ATIVIA†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTG (N=411)</td>
<td>RAL (n=411)</td>
<td>DTG (n=224)</td>
<td>DRV/r (n=242)</td>
</tr>
<tr>
<td><strong>Insomnia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>25 (6)</td>
<td>20 (5)</td>
<td>20 (8)</td>
<td>16 (7)</td>
</tr>
<tr>
<td>Severe/grade 3/4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Led to withdrawal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>17 (4)</td>
<td>23 (6)</td>
<td>13 (5)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Drug related</td>
<td>1/17 (6)</td>
<td>2/23 (9)</td>
<td>1/13 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Severe/grade 3/4</td>
<td>1/17 (6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Led to withdrawal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>29 (7)</td>
<td>21 (5)</td>
<td>16 (7)</td>
<td>12 (5)</td>
</tr>
<tr>
<td>Drug related</td>
<td>1/29 (3)</td>
<td>2/21 (10)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Severe/grade 3/4</td>
<td>1/29 (3)</td>
<td>1/21 (5)</td>
<td>3/16 (19%)</td>
<td>1/12 (8)</td>
</tr>
<tr>
<td>Led to withdrawal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Suicidality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>4 (&lt;1)</td>
<td>6 (1)</td>
<td>4 (2)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Drug related</td>
<td>0</td>
<td>0</td>
<td>1/4 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Severe/grade 3/4</td>
<td>3/4 (75)</td>
<td>5/6 (83)</td>
<td>3/4 (75)</td>
<td>0</td>
</tr>
<tr>
<td>Led to withdrawal</td>
<td>0</td>
<td>2/6 (33)</td>
<td>1/4 (25)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Selected
†All 3rd agents were part of a 3-drug regimen containing 2 NRTIs

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Adapted from reference 72
CHANGE FROM BASELINE TO 144 WEEKS IN RENAL PARAMETERS

No DTG Renal discontinuation
CHALLENGING (BUT FREQUENT) CLINICAL SCENARIOS

• Late presenter (or advance, with/out AIDS)
• Young MSM on Chem SEX (weekend; condomless behaviour)
• PHI.
• Confirmed (or perceived) poor ART adherence.
• Women on childbearing age (or not on birth control compliance) or looking for pregnancy.
• HIV patient with a long history of ARV intolerance or toxicity.
• HCV or HBV coinfection with liver fibrosis.
• Ageing patient harbouring multiple comorbidities. (or at high risk to developed).
Model Simulation Predicts Growth of Aging HIV+ Population

- By 2030, ~ 60% of HIV+ pts predicted to be older than 60 yrs of age, with ~ 10% older than 70 yrs of age

Observed (Red Box) and Projected Age Distribution of HIV+ Pts 2009-2030

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Adapted from reference 74
Comorbidities

Mean number of comorbidities:
HIV-positive: 1.3
HIV-negative: 1.0

Raised rates of:
Hypertension
MI
Peripheral arterial disease
Impaired renal function
<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Comedication</th>
<th>ART consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>Budesonide inh</td>
<td>avoid CYP3A4 inh (booster)</td>
</tr>
<tr>
<td>Diabetes mellitus (II)</td>
<td>metformin</td>
<td>Renal transporter (OCT2): DTG, RPV; TDF</td>
</tr>
<tr>
<td>HTA</td>
<td>losartan</td>
<td>booster, caution</td>
</tr>
<tr>
<td>Atrial fibrilation</td>
<td>asa; dabigatran</td>
<td>booster (contraindicated)</td>
</tr>
<tr>
<td>Renal insuficiency</td>
<td></td>
<td>booster (caution)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>atorvastatin</td>
<td></td>
</tr>
<tr>
<td>NASH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
How DTG fits into an IDEAL cART regimen criteria?

- Highly Efficacious ✓
- Safe and Well Tolerated ✓
- High Genetic Barrier to Resistance ✓
- Convenience ✓
- DDI- no/few ✓
MUITO OBRIGADO
Informações Médicas GSK
Canal de comunicação exclusivo para os Profissionais de Saúde

Artigos científicos na íntegra

Respostas a questionamentos científicos sobre os produtos GSK

Levantamentos bibliográficos relacionados às áreas terapêuticas de atuação da GSK

Bulas completas dos produtos GSK

Faça a sua solicitação através de

medinfo@gsk.com

Construindo Confiança, Promovendo Transparência
Referências Bibliográficas

21. TIVICAY® (dolutegravir sódico). Bula do produto.
Referências Bibliográficas

Referências Bibliográficas

66. ISENTRESS® (raltegravir). Bula do produto.
Material destinado exclusivamente para profissionais de saúde habilitados a prescrever ou dispensar medicamentos.

A bula completa do medicamento e outras informações estão à disposição sob solicitação ao departamento de Informações Médicas (DDG 0800 701 22 33 ou e-mail medinfo@gsk.com). Para notificar eventos adversos ocorridos durante o uso de medicamentos da GlaxoSmithKline/Stiefel, entre em contato diretamente com o Departamento de Farmacovigilância da empresa pelo e-mail farmacovigilancia@gsk.com ou através do representante do grupo de empresas GSK.