Insulin resistance, Diabetes mellitus and treatment consideration in HIV infection

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Prescribing information is available at the end of this deck
This meeting has been organised and funded by Gilead Sciences Ltd
Licensed indications for the TAF-based regimens

GENVOYA®▼ Elvitegravir 150mg, Cobicistat 150mg, Emtricitabine 200mg & Tenofovir Alafenamide 10mg
Is indicated for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35kg) infected with human immunodeficiency virus-1 (HIV-1) without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir.

ODEFSEY®▼ Rilpivirine 25mg, Emtricitabine 200mg & Tenofovir Alafenamide 25mg
Is indicated for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35kg) infected with human immunodeficiency virus-1 (HIV-1) without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine and with a viral load ≤ 100,000 HIV-1 RNA copies/mL.

DESCOVY®▼ Emtricitabine 200mg & Tenofovir Alafenamide 10mg or Emtricitabine 200mg & Tenofovir Alafenamide 25mg
Is indicated in combination with other antiretroviral agents for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35kg) infected with human immunodeficiency virus-1 (HIV-1).

TAF in the context of HIV and this presentation is referring to the co-formulated combinations outlined above.
TAF is NOT licensed for use as a single agent for the treatment of HIV infection.
Issues to discuss

- Insulin resistance, metabolic syndrome and type 2 diabetes in the general population

- Consequences of insulin resistance, metabolic syndrome and type 2 diabetes

- Management
  - Diet & exercise
  - Pharmacology
  - ART choices
Insulin facilitates the storage of energy from food after meals.

ATP, adenosine triphosphate; VLDL, very-low-density lipoprotein; TG, triglyceride
Type 2 diabetes

Two principle defects

Insulin resistance

β-Cell dysfunction/failure

± Environment

IGT

Glucose toxicity

Type 2 diabetes

Glucose toxicity

Genes

Genes

IGT

IGT

± Environment

Reaven GM. *Physiol Rev.* 1995;75:473–486


IGT, impaired glucose tolerance
Progression of type 2 diabetes

Glucose (mmol/L)

Years of diabetes

At risk for diabetes

β-Cell function

Insulin resistance

Insulin level

Postmeal glucose

Fasting glucose

Converted from US units

Adapted from Kendall D, Bergenstal R. © International Diabetes Center (2010)
Major risk factors for type 2 diabetes

- First degree relative with type 2 diabetes
- Obesity (>20% over ideal body weight)
- Race/ethnicity (Hispanics, African, Native Americans, Asian, Pacific Islanders)
- Age > 45 years
- Prior impaired fasting glucose or impaired glucose tolerance
- Hypertension
- Dyslipidaemia
- History of gestational diabetes or large-for-gestational-age baby (>9 lbs)

Clinical evaluation of glucose metabolism

Fasting Glucose  HOMA Index  OGTT  IVGTT  Euglycaemic Clamp

Sensitivity

HOMA, homeostatic model assessment; QUICKI, quantitative insulin sensitivity check; OGTT, oral glucose tolerance test; IVGTT, intravenous glucose tolerance test
Diagnostic criteria for glycaemic abnormalities

<table>
<thead>
<tr>
<th>FPG (mg/dL)</th>
<th>Haemoglobin A1C (%)</th>
<th>2-Hour PG on OGTT (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>126</td>
<td>7.0</td>
<td>11.1</td>
</tr>
<tr>
<td>100</td>
<td>5.6</td>
<td>140</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

To convert mg/dL to mmol/L multiply mg/dl by 0.055

FPG, fasting plasma glucose; PG, plasma glucose; OGTT, oral glucose tolerance test

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2001;24:S5–S20
American Diabetes Association. *Diabetes Care* 2010;33:S11-61
# ADA and AACE glycaemic treatment goals

<table>
<thead>
<tr>
<th>Biochemical Index</th>
<th>Normal</th>
<th>Goal</th>
<th>Action Suggested</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting/preprandial plasma glucose (mmol/L)</td>
<td>&lt;6.1</td>
<td>5–7.2</td>
<td>&lt;5 or &gt;8.3</td>
<td>≤6.1</td>
</tr>
<tr>
<td>Postprandial plasma glucose (mmol/L)</td>
<td>&lt;7.8</td>
<td>&lt;9.9</td>
<td>NA</td>
<td>≤7.8</td>
</tr>
<tr>
<td>Bedtime plasma glucose (mmol/L)</td>
<td>&lt;6.7</td>
<td>6.1–8.3</td>
<td>&lt;6.1 or &gt;9.9</td>
<td>NA</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>&lt;6</td>
<td>&lt;7</td>
<td>&gt;8</td>
<td>≤6.5</td>
</tr>
</tbody>
</table>

Converted from US units

ADA, American Diabetes Association; AACE, American Association of Clinical Endocrinologists; A1C, glycated haemoglobin


American College of Endocrinology. *Endocr Pract*. 2007;13(Suppl1)
Diabetes: risk of myocardial infarction

Patients with DM but no CHD experience a similar rate of MI as patients without DM but with CHD

*Fatal or non-fatal MI

CHD, coronary heart disease; DM, diabetes mellitus; MI, myocardial infarction

Insulin resistance and HIV

Classical type 2 diabetes risk factors:
- Obesity (abdominal)
- Physical inactivity
- Genetic
  - Family history
  - Race
- Older age
- Dyslipidaemia

HIV-associated risk factors:
- NRTI mitochondrial toxicity
- PI and GLUT inhibition
- Dyslipidaemia
- Peripheral lipoatrophy
- Increased liver or muscle fat
- Inflammatory cytokines
- Low testosterone
- HCV infection

Moyle, G. Personal Communication
Increasing prevalence in diabetes with age in both HIV and non-HIV populations

- DM diagnosed by ICD-9 codes
- 7219 HIV (61% male) and 2,792,971 non-HIV (30% male) individuals, for a total 7,101,180 person-years

DM incidence rates (per 100 person-years)

<table>
<thead>
<tr>
<th>Age group</th>
<th>HIV</th>
<th>Non-HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–24</td>
<td>6.1</td>
<td>2.9</td>
</tr>
<tr>
<td>25–34</td>
<td>8.1</td>
<td>4.2</td>
</tr>
<tr>
<td>35–44</td>
<td>10.5</td>
<td>6.7</td>
</tr>
<tr>
<td>45–54</td>
<td>11.9</td>
<td>7.7</td>
</tr>
<tr>
<td>55–64</td>
<td>13.3</td>
<td>8.3</td>
</tr>
<tr>
<td>65+</td>
<td>9.7</td>
<td>5.0</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus

Currier J, et al. 9th CROI, Seattle 2002, #677
Diabetes mellitus incidence is increased in HIV-infected patients on HAART

Diabetes mellitus is more than 4 times higher in HIV-infected patients on HAART as compared to the general population.

<table>
<thead>
<tr>
<th>Patients free of diabetes mellitus (%)</th>
<th>Study time, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Seronegative</td>
<td>0</td>
</tr>
<tr>
<td>HIV Infected Using HAART</td>
<td>265</td>
</tr>
<tr>
<td></td>
<td>177</td>
</tr>
<tr>
<td></td>
<td>89</td>
</tr>
<tr>
<td>HIV Infected Using HAART</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>204</td>
</tr>
<tr>
<td></td>
<td>145</td>
</tr>
<tr>
<td></td>
<td>62</td>
</tr>
</tbody>
</table>

Per unit gain in BMI associated with ~20% increased risk of CVD in those with pre-ART BMI in middle 2 quartiles; those at extremes did not experience any appreciable increase in their CVD risk.
FRAM: VAT and upper trunk SAT are associated with insulin resistance

Asterisks denote comparison with first tertile:

- *** $P<0.0001$
- ** $P<0.001$
- * $P<0.01$
- + $P<0.05$

Multivariable Analysis

Men and Women

HOMA (95% CI) adjusted geometric mean

VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue

Association between limb fat and insulin resistance in lipoatrophy

*P<0.05 compared with controls and HIV-infected groups

LBM, lean body mass

Lipotoxicity: muscle fat and insulin resistance in HIV

Increased intramyocellular TG concentration (evaluated by proton-MRS) inversely related to insulin sensitivity in HIV-LD (●) and controls (○) subjects.

\[ r^2 = 0.27; \ P = 0.0093 \]

Hepatic insulin resistance is associated with hepatic steatosis

Liver fat content (evaluated by proton-MRS) was related to insulin resistance in HIV-LD (●) and control (○) subjects.
Traditional risk factors contribute similarly to CV risk in HIV+ and HIV-

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Unit</th>
<th>Iloje, HIV Med 2005</th>
<th>Friis-Moller et al. DAD NEJM 2003</th>
<th>HIV negative (# studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Per 1 year older</td>
<td>9%</td>
<td>6%</td>
<td>6–9% (7)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male vs female</td>
<td>NA</td>
<td>110%</td>
<td>110–160% (2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes vs no</td>
<td>260%</td>
<td>90%</td>
<td>140–252% (3)</td>
</tr>
<tr>
<td>Smoking</td>
<td>Yes vs no</td>
<td>140%</td>
<td>290%</td>
<td>70–290% (3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes vs no</td>
<td>30%</td>
<td>80%</td>
<td>80–90% (3)</td>
</tr>
</tbody>
</table>

Adapted from Currier JS, Lundgren JD et al. Circulation 2008;118:198-210
D:A:D relationship between exposure to individual drugs and incidence of DM

The incidence of DM in D:A:D is 5.72 per 1000 PYFU

<table>
<thead>
<tr>
<th>Cumulative exposure</th>
<th>Relative risk</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stavudine (per year)</td>
<td>1.19</td>
<td>1.15–1.24</td>
<td>0.0001</td>
</tr>
<tr>
<td>Zidovudine (per year)</td>
<td>1.06</td>
<td>1.03–1.10</td>
<td>0.0004</td>
</tr>
<tr>
<td>Didanosine (per year)</td>
<td>1.06</td>
<td>1.02–1.11</td>
<td>0.01</td>
</tr>
<tr>
<td>Ritonavir (per year)</td>
<td>0.94</td>
<td>0.89–0.99</td>
<td>0.01</td>
</tr>
<tr>
<td>Nevirapine (per year)</td>
<td>0.89</td>
<td>0.84–0.95</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, BMI, race, smoking status, calendar year, and cohort.

# NNT to Harm with MI: ABC in D:A:D

<table>
<thead>
<tr>
<th>Risk</th>
<th>Underlying 5 year risk (%)</th>
<th>5 year NNH</th>
<th>Underlying 10 year risk (%)</th>
<th>10 year NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (40 yo non-smoker with good lipids and BP)</td>
<td>0.1</td>
<td>1111</td>
<td>0.3</td>
<td>370</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.4</td>
<td>277</td>
<td>1.5</td>
<td>92</td>
</tr>
<tr>
<td>Smoker and DM</td>
<td>1.1</td>
<td>101</td>
<td>3.1</td>
<td>35</td>
</tr>
<tr>
<td>Smoker and raised lipids</td>
<td>3.1</td>
<td>35</td>
<td>7.5</td>
<td>14</td>
</tr>
<tr>
<td>Previous CVD</td>
<td>5</td>
<td>22</td>
<td>10</td>
<td>14</td>
</tr>
</tbody>
</table>

NNT, number needed to harm; MI, myocardial infarction; ABC, abacavir; DM, diabetes mellitus; CVD, cardiovascular disease

HIV disease, ART, insulin resistance and diabetes mellitus

Impact of individual drug choice on insulin sensitivity
GLUT4: The insulin induced transporter of glucose

IRS, insulin receptor substrate; PI-3 Kinase, phosphoinositide-3 kinase
Impact on insulin sensitivity: ATV/RTV and LPV/RTV

Boosted ATV Study\(^1\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change in insulin-stimulated glucose disposal rate at Day 10 (%)</th>
<th>n</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/RTV 300/100 mg</td>
<td>-10</td>
<td>24</td>
<td>P=0.132</td>
</tr>
<tr>
<td>LPV/RTV 400/100 mg</td>
<td>-25</td>
<td>24</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

P=0.023

ATV, Atazanavir; RTV, Ritonavir; LPV, Lopinavir

Insulin resistance with PI/r and EVG/c + TDF/FTC

Glucose disposal* (mg glucose/min*kg)

- **LPV/r**
  - Baseline: 8.2
  - Week 2: 13.3
  - P = 0.036

- **DRV/r**
  - Baseline: 9.8
  - Week 2: 9.8
  - P = NS

- **EVG/c**
  - Baseline: 9.8
  - Week 2: 9.8
  - P = NS

*Refers to glucose disposal following hyperinsulinaemic euglycaemic clamp before and 14 days after start of ART

Insulin levels in the FIRST study

- PI vs NNRTI vs PI+NNRTI
- PI: slight early increase
- All: increase later
- ddI+d4T vs ABC+3TC
- ddI+d4T is worse

<table>
<thead>
<tr>
<th>PI</th>
<th>Change (unit/month)</th>
<th>SE</th>
<th>P - Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.07</td>
<td>0.02</td>
<td>&lt;0.005</td>
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<table>
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<th>Change (unit/month)</th>
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<th>P - Value</th>
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<td>&lt;0.005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PI + NNRTI</th>
<th>Change (unit/month)</th>
<th>SE</th>
<th>P - Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.08</td>
<td>0.02</td>
<td>&lt;0.005</td>
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<th>Change (unit/month)</th>
<th>SE</th>
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<td>0.02</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ddI+d4T</th>
<th>Change (unit/month)</th>
<th>SE</th>
<th>P - Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.12</td>
<td>0.09</td>
<td>0.57</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ABC+3TC</th>
<th>Change (unit/month)</th>
<th>SE</th>
<th>P - Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.05</td>
<td>0.09</td>
<td></td>
</tr>
</tbody>
</table>

No impact of tenofovir DF on insulin sensitivity and lipids in healthy volunteers

Mean values are presented with (SD)

$P$-value obtained using Wilcoxon signed rank tests

Tenofovir DF significantly reduces total cholesterol and LDL-c

<table>
<thead>
<tr>
<th>Lipid Parameter</th>
<th>Baseline</th>
<th>Placebo</th>
<th>TDF 4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>5.0</td>
<td>5.0</td>
<td>3.0</td>
</tr>
<tr>
<td>HDL</td>
<td>4.0</td>
<td>4.0</td>
<td>3.0</td>
</tr>
<tr>
<td>LDL</td>
<td>3.0</td>
<td>3.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>2.0</td>
<td>2.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

P values:
- Total Cholesterol: 0.004
- HDL: 0.017
- LDL: 0.025
- Triglycerides: 0.025

No impact of raltegravir vs. reduction in insulin sensitivity with LPV/r in healthy volunteers

Mean Percentage Change – Glucose Disposal Rate

P = 0.018

Error bars: 95% CI. P - value obtained using independent t test assuming equal variance.

LPV, Lopinavir

Multivariate Analyses Examining Effects of Treatment and Clinical Characteristics on Change in Glucose and HOMA-IR Over 96 Weeks

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Reference</th>
<th>96-Week Glucose Change (mg/dL)</th>
<th>96-Week HOMA-IR Fold Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC/3TC</td>
<td>TDF/FTC</td>
<td>0.18</td>
<td>0.80</td>
</tr>
<tr>
<td>EFV</td>
<td>ATV/r</td>
<td>&lt;0.001</td>
<td>0.61</td>
</tr>
<tr>
<td>Baseline HIV-1 RNA</td>
<td>Continuous (per 1 Log_{10} copies/ml higher)</td>
<td>0.047</td>
<td>0.023</td>
</tr>
<tr>
<td>96-week BMI Change</td>
<td>Continuous (per 1 kg/m^2 higher)</td>
<td>0.005</td>
<td></td>
</tr>
</tbody>
</table>

HOMA-IR, homeostatic model assessment – insulin resistance; ABC/3TC, abacavir/lamivudine; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine EFV, efavirenz; ATV/r, atazanavir/ritonavir

Erlandson K, et al. 21st CROI; Abst. 772
Interventions for pre-DM & DM

- Diet & Exercise, Smoking cessation
- Weight reduction
- Pharmacological
  - Sulfonylureas: gliclazide
  - Biguanides: metformin
  - Thiazolidinediones (glitazones): rosiglitazone or pioglitazone
  - Gliptins
  - Insulin
- ARB or ACE inhibitor for renal protection
- Statin and other lipid lowering agents
- Anticoagulant
- Modification of ART

ARB, angiotensin receptor blockers; ACE, angiotensin-converting enzyme
Medical and surgical interventions shown to delay or prevent T2D

Lifestyle modification should be used with all pharmacologic or surgical interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Follow-up Period</th>
<th>Reduction in Risk of T2D ((P) value vs placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antihyperglycemic agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin(^1)</td>
<td>2.8 years</td>
<td>31% ((P&lt;0.001))</td>
</tr>
<tr>
<td>Acarbose(^2)</td>
<td>3.3 years</td>
<td>25% ((P=0.0015))</td>
</tr>
<tr>
<td>Pioglitazone(^3)</td>
<td>2.4 years</td>
<td>72% ((P&lt;0.001))</td>
</tr>
<tr>
<td>Rosiglitazone(^4)</td>
<td>3.0 years</td>
<td>60% ((P&lt;0.0001))</td>
</tr>
<tr>
<td><strong>Weight loss interventions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orlistat(^5)</td>
<td>4 years</td>
<td>37% ((P=0.0032))</td>
</tr>
<tr>
<td>Phentermine/topiramate(^6)</td>
<td>2 years</td>
<td>79% ((P&lt;0.05))</td>
</tr>
<tr>
<td>Bariatric surgery(^7)</td>
<td>10 years</td>
<td>75% ((P&lt;0.001))</td>
</tr>
</tbody>
</table>


T2D, type 2 diabetes
What happens after DM diagnosis?

New medication
- Dietary changes
- Metformin
- Statin
- Antihypertensive (ARB or ACE)
- Anticoagulant

New monitoring
- Blood sugar
- HbA1c
- Urinary albumin, ACR, eGFR
- BP
- Retinal screens
- Neuropathy screens
- Podiatry

ARB, angiotensin receptor blockers; ACE, angiotensin-converting enzyme; HbA1c, glycated haemoglobin; ACR, albumin/creatinine ratio; eGFR, estimated glomerular filtration rate; BP, blood pressure
Benefits of exercise and dietary changes in the metabolic syndrome

A 6-month, randomised trial in HIV-infected subjects with NCEP defined metabolic syndrome receiving lifestyle modification (n=16) or observation (n=18)

Systolic Blood Pressure

-20 -15 -10 -5 0 5 10

mm Hg

P=0.008

Waist Circumference

-4 -3 -2 -1 0 1 2 3

cm

P=0.022

Fitch K, et al. AIDS. 2006;20:1843-50

NCEP, National Cholesterol Education Program
Metformin patients lost weight and had decreased waist circumference.

Hadigan C et al. JAMA. 2000;284:472-477

![Graph showing weight and waist circumference changes with Metformin and Placebo groups](image-url)
**Prediabetes algorithm**

**Lifestyle modification**
(including Medically assisted Weight Loss)

**Other CVD risk factors**

**Weight loss therapies**

**CVD risk factor modifications algorithm**

- Dyslipidaemia route
- Hypertension route

**Antihyperglycaemic therapies**

- FPG > 100 | 2-hour PG > 140

**Normal glycaemia**

- Progression

**Overt diabetes**

- Intensify weight loss therapies

**1 Pre-DM criterion**

- Low-risk medications
  - Metformin
  - Acarbose

**Multiple pre-DM criteria**

- Consider with caution
  - TZD
  - GLP-1 RA

If glycaemia not normalised, consider with caution

---

AACE/ACE Comprehensive Diabetes Management Algorithm, *Endocr Pract.* 2015;21(No. 4)
Current oral therapies address different metabolic defects in type 2 diabetes

- **Glucose influx**
  - α-Glucosidase inhibitors
  - Metformin

- **Insulin resistance**
  - TZDs

- **Glucagon secretion**
  - Metformin

- **Insulin demand**
  - TZDs

- **Insulin supply**
  - Acute β-cell function
    - Sulfonylureas
  - Chronic β-cell function
    - Glinides

TZDs, thiazolidinediones
The effect of dolutegravir on the pharmacokinetics of metformin in healthy subjects

Zong, Jian¹; Borland, Julie²; Jerva, Fred²; Wynne, Brian³; Choukour, Mike⁴ and Song, Ivy¹

¹Clinical Pharmacology Modeling & Simulation, GlaxoSmithKline, RTP, USA. ²CPSSO, GlaxoSmithKline, RTP, USA. ³Infectious Disease MDD, GlaxoSmithKline, RTP, USA. ⁴Biostatistics, Parexel, Sarasota, FL, USA.

Conclusions: Co-administration of DTG and metformin was well tolerated, yet significantly increased metformin plasma exposure; effects were DTG dose dependent. Though metformin has a wide therapeutic index and alone is not associated with hypoglycemia, close monitoring is recommended when co-administering metformin and DTG. Dose adjustments of metformin may be considered.

Table 1. Statistical comparison of metformin PK parameters with and without dolutegravir

<table>
<thead>
<tr>
<th>Plasma Metformin PK Parameter</th>
<th>GLS mean Metformin Alone (Period 1)</th>
<th>GLS mean Metformin + DTG (Period 2)</th>
<th>GLS mean ratio (90% CI) Metformin + DTG vs. Metformin Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1 (DTG 50 mg QD)</td>
<td>n = 15</td>
<td>n = 14</td>
<td>1.66 (1.53, 1.81)</td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>0.932</td>
<td>1.55</td>
<td></td>
</tr>
<tr>
<td>AUC(0-τ) (hr*µg/mL)</td>
<td>6.83</td>
<td>12.2</td>
<td>1.79 (1.65, 1.93)</td>
</tr>
<tr>
<td>Cohort 2 (DTG 50 mg BID)</td>
<td>n = 15</td>
<td>n = 14</td>
<td>2.11 (1.91, 2.33)</td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>0.845</td>
<td>1.878</td>
<td></td>
</tr>
<tr>
<td>AUC(0-τ) (hr*µg/mL)</td>
<td>6.49</td>
<td>15.9</td>
<td>2.45 (2.25, 2.66)</td>
</tr>
</tbody>
</table>
Blood pressure targets

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>Individualize on the basis of age, comorbidities, and duration of disease, with general target of:</td>
</tr>
<tr>
<td>Systolic, mm Hg</td>
<td>~130</td>
</tr>
<tr>
<td>Diastolic, mm Hg</td>
<td>~80</td>
</tr>
</tbody>
</table>

- A more intensive goal (such as <120/80 mm Hg) should be considered for some patients, provided the target can be safely reached without adverse effects from medication.
- ACE or ARB provide greatest renal protective effects.

ARB, angiotensin receptor blockers; ACE, angiotensin-converting enzyme

NICE. Hypertension in adults: clinical guidelines. 2011
Available at: https://www.nice.org.uk/guidance/cg127
Blood pressure treatment

- Employ therapeutic lifestyle modification
  - DASH or other low-salt diet combined with physical activity

- Select antihypertensive medications based on BP-lowering effects and ability to slow progression of nephropathy and retinopathy
  - ACE inhibitors or ARBs

- Add additional agents when needed to achieve blood pressure targets
  - Calcium channel antagonists
  - Diuretics preferably Indapamide
  - Combined α/β-adrenergic blockers
  - β-adrenergic blockers
  - Do not combine ACE inhibitors with ARBs

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure; DASH, Dietary Approaches to Stop Hypertension

NICE. Hypertension in adults: clinical guidelines. 2011 Available at: https://www.nice.org.uk/guidance/cg127
Statin use

- Should be universally considered
- LDL-C target: <70 mmol/L or 3 mmol/l—for DMs
- Atorvastatin, Rosuvastatin and Pitavastatin
- Watch for ART interactions

Use a statin regardless of LDL-C level in patients with diabetes who meet the following criteria:
- >40 years of age
- ≥1 major ASCVD risk factor
  - Hypertension
  - Family history of CVD
  - Low HDL-C
  - Smoking

ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; HDL-C, high density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol

**Lipid targets**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderate risk</td>
</tr>
<tr>
<td><strong>Primary goals</strong></td>
<td></td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>&lt;5.5</td>
</tr>
<tr>
<td>Non–HDL-C, mmol/L</td>
<td>&lt;7.2</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>&lt;8.3</td>
</tr>
<tr>
<td>TC/HDL-C ratio</td>
<td>&lt;3.5</td>
</tr>
<tr>
<td><strong>Secondary goals</strong></td>
<td></td>
</tr>
<tr>
<td>ApoB, mmol/L</td>
<td>&lt;5</td>
</tr>
<tr>
<td>LDL particles</td>
<td>&lt;1,200</td>
</tr>
</tbody>
</table>

- Moderate risk = diabetes or prediabetes with no ASCVD or major CV risk factors
- High risk = established ASCVD or ≥1 major CV risk factor
- CV risk factors
  - Hypertension
  - Family history
  - Low HDL-C
  - Smoking

ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; HDL-C, high density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol

Converted from US units

Antiplatelet agents

Consider aspirin therapy (75–162 mg/day)

- Meta-analysis suggests no/limited benefit in diabetes
- Greater benefits may exist in those who have at least one additional major risk factor
  - Known vascular disease, retinopathy or nephropathy
  - Family history of cardiovascular disease
  - Hypertension
  - Smoking
  - Dyslipidemia
  - Albuminuria

Adapted from ADA. VI. Prevention, Management of Complications. Diabetes Care 2014;37(suppl 1):S40
## Estimated 5 year NNT with statin by CAC

<table>
<thead>
<tr>
<th>CAC Group</th>
<th>Estimated CHD event rate at 7.6 years</th>
<th>Estimated CVD event rate at 7.6 years</th>
<th>5-year NNT CHD</th>
<th>5-year NNT CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAC = 0</td>
<td>1.49%</td>
<td>5.47%</td>
<td>486</td>
<td>132</td>
</tr>
<tr>
<td>CAC 1–100</td>
<td>12.08%</td>
<td>16.33%</td>
<td>60</td>
<td>44</td>
</tr>
<tr>
<td>CAC &gt;100</td>
<td>18.77%</td>
<td>26.57%</td>
<td>39</td>
<td>27</td>
</tr>
</tbody>
</table>

**NNT calculated using 21% RR reduction**

CAC, coronary artery calcification; CHD, congenital heart defect; CVD, cardiovascular disease; NNT, number needed to treat


Rosuvastatin vs. placebo in HIV: effects on BMD, and insulin, inflammation (Saturn N=147)

Changes in BMD at Wk 48

- No differences reported in spine BMD
- Trochanter BMD: Rosuvastatin -0.7%, Placebo 1.0%
- Hip BMD: Rosuvastatin 0%, Placebo 20%

Insulin Sensitivity

- Rosuvastatin significantly lowered sTNF, sCD14, fibrinogen and activated CD4 and CD8

Atorvastatin vs placebo for non-Ca++ coronary plaques

- 40 HIV-infected pts with subclinical coronary atherosclerosis and low density lipoprotein (LDL) cholesterol <7.2mmol/L

- Coronary atherosclerotic plaque as assessed by coronary computed tomography angiography

- Statin therapy was well-tolerated, with low incidence of clinical adverse events or laboratory abnormalities

Changes in non-calcified plaque and key lipids

<table>
<thead>
<tr>
<th>NC Plaque %</th>
<th>LDL-c mg/dl</th>
<th>Lpa ng/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lo J, et al. 22nd CROI; 2015. Abst. 136
SATURN: rosuvastatin & carotid intimal media thickening (CIMT) in treated HIV

Longenecker C, et al. 22nd CROI; 2015. Abst. 137

<table>
<thead>
<tr>
<th></th>
<th>Mean 96 Week Change</th>
<th>95% Confidence Interval</th>
<th>Within Group P-value</th>
<th>Between Group P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>+0.028mm</td>
<td>0.008–0.047</td>
<td>0.006</td>
<td>0.074</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>+0.003mm</td>
<td>-0.014–0.021</td>
<td>0.714</td>
<td></td>
</tr>
</tbody>
</table>
Assessment of diabetic nephropathy

- Annual assessments
  - Serum creatinine to determine eGFR
  - Urine Albumin/Creatinine ratio

- Begin annual screening
  - 5 years after diagnosis of T1D if diagnosed before age 30 years
  - At diagnosis of T2D or T1D in patients diagnosed after age 30 years

- HIV:
  - caution with DTG, RPV, /r and /c regards effects on eGFR
  - Caution with TDF re renal effects on eGFR and tubular proteins including albumin
  - Caution with ABC due to CV risk in high risk patients
  - Caution with ATV/r and /c due to kidney stones
Urinary proteins

- Large (albumin) and small/low molecular weight proteins (such as B2M, RBP) are filtered at glomerulus
  - Therefore, protein especially albumin in urine is considered evidence of glomerular disease in DM and H/T

- Tubules reabsorb low molecular weight proteins and some albumin
  - Therefore, tubular dysfunction increases protein in the urine and may ‘mislead’

- Presence of albumin in the urine is a risk factor for CV events

B2M, β-2 microglobulin; RBP, retinol-binding protein; H/T, hypertension; CV, cardiovascular disease
ASSERT: adjusted mean change from baseline in eGFR

**ABC/3TC and TDF/FTC in combination with EFV minimally affected estimated glomerular filtration rate over 96 weeks**


ABC/3TC, abacavir/lamivudine; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

EFV, efavirenz
SPRING: DTG vs RAL
Change from baseline in creatinine over time by NRTIs

Mean change from baseline in creatinine (µmol/L)

Week

Mean (±SD)

Curtis L, et al. 7th IAS; 2013; Abstract TUE282
Studies 104 and 111: week 48 combined analysis

TAF vs TDF with E/C/F: renal safety

<table>
<thead>
<tr>
<th>Events</th>
<th>E/C/F/TAF n=866</th>
<th>E/C/F/TDF n=867</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal adverse events leading to discontinuation</td>
<td>0</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Tubulopathy/Fanconi syndrome</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Sax P, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 143LB
Studies 104 and 111: ART-naïve patients, week 48 combined analysis

Changes (%) in quantitative proteinuria at week 48

Baseline ratios

-4.97* mg/mmol
-4.97* mg/mmol
-0.57† mg/mmol
-0.57† mg/mmol
-7.23^ μg/mmol
-7.57** μg/mmol
-11.41†† μg/mmol
-11.64^^ μg/mmol

E/C/F/TAF
E/C/F/TDF

Significantly less proteinuria with E/C/F/TAF vs E/C/F/TDF


ß-2 µglobulin, beta-2 microglobulin
Study 109: suppressed adults switched from a TDF-containing regimen to E/C/F/TAF

Changes (%) in quantitative proteinuria at week 48

Switching to E/C/F/TAF from a regimen containing FTC/TDF+3rd agent resulted in significant decreases in proteinuria, albuminuria, and tubular proteinuria at Week 48

CR; creatinine, UPCR; urine protein/creatinine ratio, UACR; urine albumin/creatinine ratio, RBP; retinol-binding protein, β-2-µ; beta-2 microglobulin.

Mills A et al. IAS 2015,, Canada. Oral # TUAB0102
Study 112: suppressed adults with renal impairment switched to E/C/F/TAF

Changes in eGFR through week 48

<table>
<thead>
<tr>
<th>Baseline eGFR&lt;sub(CG&lt;/sub&gt; 30–49 mL/min</th>
<th>Baseline eGFR&lt;sub(CG&lt;/sub&gt; 50–69 mL/min</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Change in eGFR (Cockcroft-Gault) by baseline eGFR&lt;sub(CG&lt;/sub&gt;</th>
<th>Change in eGFR (CKD-EPI, cystatin C) by baseline eGFR&lt;sub(CG&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline eGFR&lt;sub(CG&lt;/sub&gt; 30–49 mL/min</td>
<td>Baseline eGFR&lt;sub(CG&lt;/sub&gt; 50–69 mL/min</td>
</tr>
</tbody>
</table>

Primary endpoint
Median (IQR) change at Week 24
-0.4 (-4.8, 4.5) mL/min

3.8 (-4.8, 11.2) mL/min/1.73 m²

No notable changes in eGFR<sub(CG</sub> or eGFR<sub(CKD-EPI, cystatin C</sub> through Week 48

Pozniak A et al. CROI 2015. #795
Changes in proteinuria status at Week 48

Baseline status:
- Non-significant proteinuria at BL
  - n=127
- Significant proteinuria at BL
  - n=88

Changes in proteinuria status at Week 48:
- Worsened*:
  - 7/127
- Improved**:
  - 61/88

Substantial improvements in clinically significant proteinuria and albuminuria at Week 48

Changes in albuminuria status at Week 48

- Non-significant albuminuria at BL: n=110
- Significant albuminuria at BL: n=104

Changes in albuminuria status at Week 48:
- Worsened*:
  - 6/110
- Improved**:
  - 55/104

*Worsened = change from non-significant to clinically significant UPCR (>200 mg/g or 22.6 mg/mmol) or UACR (≥30 mg/g or 3.36 mg/mmol)

**Improved = change from clinically significant to non-significant UPCR (<200 mg/g or 22.6 mg/mmol) or UACR (<30 mg/g or 3.36 mg/mmol)

UPCR = urine protein to creatinine ratio; UACR = urine albumin to creatinine ratio

†Change from baseline was statistically significant (P<0.001)
Renal impairment switch study

Phase 3, multicenter, open-label study of virologically suppressed adults with stable eGFR_{CG} (30–69 mL/min) switching to E/C/F/TAF

Key inclusion criteria:
- CD4 cell count $\geq 50$ cells/μL
- No chronic hepatitis B or C virus infection
- HIV-1 RNA <50 copies/mL for $\geq 6$ months

All have eGFR_{CG} 30–69 mL/min

With Diabetes n=33

Without Diabetes n=209

Primary endpoint: Change from baseline in eGFR

Week 0 24 48 96 144

Efficacy and Renal Outcomes by Baseline Diabetes Status

E/C/F/TAF QD

Post F, et al. CROI 2016, Abs 680

eGFR, estimated glomerular filtration rate; E/C/F/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
Results: \( eGFR_{\text{CKD-EPI,sCr}} \)
Changes from baseline to week 96

<table>
<thead>
<tr>
<th>Week</th>
<th>With Diabetes</th>
<th>Without Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>53.0 (42.0, 62.4)</td>
<td>54.2 (46.3, 62.8)</td>
</tr>
<tr>
<td>8</td>
<td>55.6 (41.4, 66.6)</td>
<td>55.1 (48.1, 63.8)</td>
</tr>
</tbody>
</table>

*Baseline vs Week 96 (2-sided Wilcoxon signed-rank test).
Results: \( \text{eGFR}_{\text{CKD-EPI,cysC}} \)

Changes from baseline to week 96

<table>
<thead>
<tr>
<th>Week</th>
<th>Baseline</th>
<th>Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>208</td>
<td>194</td>
</tr>
<tr>
<td>4</td>
<td>205</td>
<td>192</td>
</tr>
<tr>
<td>8</td>
<td>206</td>
<td>189</td>
</tr>
<tr>
<td>12</td>
<td>203</td>
<td>189</td>
</tr>
<tr>
<td>16</td>
<td>201</td>
<td>185</td>
</tr>
<tr>
<td>24</td>
<td>201</td>
<td>184</td>
</tr>
<tr>
<td>36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median, mL/min/1.73 m² (Q1, Q3)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>With Diabetes</td>
<td>69.7 (52.6, 78.9)</td>
<td>68.0 (50.3, 84.1)</td>
</tr>
<tr>
<td>Without Diabetes</td>
<td>70.0 (56.6, 83.5)</td>
<td>76.8 (61.1, 91.6)</td>
</tr>
</tbody>
</table>

*Baseline vs Week 96 (2-sided Wilcoxon signed-rank test).
Results: renal biomarkers
Changes from baseline to week 96

All changes statistically significant, with exception of UACR in diabetic patients (p=0.09).

B2m, β2-microglobulin; RBP, retinol-binding protein
Results: albuminuria
Changes from baseline to week 96

Median UACR, mg/g (Q1,Q3)

Week

0 4 8 12 16 24 36

With Diabetes
Without Diabetes

Normal range

n= 31 31 33 33 33 33 32 33 33 33 32 31

Post F, et al. CROI 2016, Abs 680
Mr DM: history

54 year old male
HIV+ since 1998
Started on AZT/3TC/EFV in 1998
Switched to TDF/FTV/EFV in 2004
Presents as new onset DM

Case was a pre-emptive switch ahead of toxicity. Any adverse events would have been reported via appropriate channels.
Mr DM: laboratory

VL <20 copies/ml, CD4 686 cells/μL
eGFR 58 ml/min
UPCR 38 mg/mmol
UACR 7 mg/mmol
BP 142/87 mm Hg
TC 5.8 mmol/l, HDL 0.95 mmol/l, TG 2.6 mmol/l
CAC 23 (50th centile)

Case was a pre-emptive switch ahead of toxicity. Any AEs would have been reported via appropriate channels.
Mr DM: actions

Change off EFV due to potential DDIs, effects on lipids, effects of insulin resistance

Change off TDF due to effects on eGFR and urinary proteins

Start: TAF/FTC/RPV

Atorvastatin 10mg od, adjusting up

Telmisartan 20mg, adjusting up

Metformin 500mg bd, adjusting up

No need for anticoagulant

Involve GP and specialist DM team. Remind the team that RPV may reduce eGFR by 4–6 units.

Provide Liverpool drug interaction website details.

Case was a pre-emptive switch ahead of toxicity. Any AEs would have been reported via appropriate channels.
Conclusions

- Diabetes, Insulin Resistance and the Metabolic Syndrome are associated with increased risks of morbidity and mortality.

- HIV-infected patients are at increased risk for diabetes, insulin resistance and MS. ARV choice may influence this risk.

- Many HIV drugs are not suitable for diabetics due to interactions, increased CVD risk, increased insulin resistance or impact on eGFR and urinary albumin.

ARV, antiretroviral; CV cardiovascular disease; eGFR, estimated glomerular filtration rate
Key points

- Diet, exercise, & education: foundation of any T2DM therapy programme

- **Metformin** remains the optimal first-line drug

- After metformin, data are limited. Combination therapy with 1–2 other oral / injectable agents is reasonable

- Many patients will require insulin therapy alone or in combination with other agents to maintain BG control

- Comprehensive CV risk reduction is a major focus of therapy
Prescribing information for Descovy

Consult the Summary of Product Characteristics (SPC) before prescribing. Descovy®
emtricitabine 200mg/tenofovir alafenamide 10mg or 25mg film coated tablets.

**Indication:** In combination with other antiretroviral agents for the treatment of HIV-1 infection in adults & adolescents (aged 12 years & older weighing at least 35 kg). Dosage: Adults & adolescents (aged ≥ 12 years, weighing at least 35 kg): One tablet, once daily, orally with or without food. The dose of Descovy should be administered according to the third agent in the HIV treatment regimen. Please consult the SPC for further information. Children (< 12 years or weighing < 35kg): Safety & efficacy has not been established. Elderly: No dose adjustment is required. Renal: No dose adjustment is required in adult or adolescent patients (aged ≥ 12 years, weighing at least 35 kg) with estimated creatinine clearance (CrCl) ≥ 30 mL/min. In patients with CrCl < 30 mL/min: not recommended. Should be discontinued in patients whose CrCl declines to < 30 mL/min during treatment. Hepatic: no dose adjustment required. Contraindications: Hypersensitivity to the active substances or to any excipients. Warnings & Precautions: Safety & efficacy in HBV/HCV co-infection has not been established. Co-infected HIV/HBV patients should be closely monitored for at least several months following discontinuation for symptoms of severe acute exacerbations of hepatitis. Descovy should be avoided in antiretroviral patients with HIV-1 harbouring the K65R mutation. Risks of mitochondrial dysfunction, immune reactivation syndrome, opportunistic infections, osteonecrosis with CART therapy. Interactions: Co-administration with certain anticonvulsants (eg. carbamazepine, oxcarbazepine, phenobarbital & phenytoin), antimycobacterials (eg. rifampicin, rifabutin & rifapentine), boceprevir, telaprevir, St. John’s wort and HIV PIs other than atazanavir, lopinavir and darunavir is not recommended. Should not be administered concomitantly with medicines containing tenofovir disoproxil, emtricitabine, lamivudine or adefovir dipivoxil. Co-administration of emtricitabine with medicinal products that are eliminated by active tubular secretion may increase concentrations of emtricitabine. Medicinal products that decrease renal function may increase concentrations of emtricitabine. Medicinal products that induce P-glycoprotein (P-gp) are expected to decrease the absorption of tenofovir alafenamide, resulting in decreased plasma concentration of tenofovir alafenamide, which may lead to loss of therapeutic effect of Descovy and development of resistance. Co-administration with medicinal products that inhibit P-gp are expected to increase the absorption and plasma concentration of tenofovir alafenamide. Tenofovir alafenamide is a substrate of OATP1B1 and OATP1B3 in vitro. The distribution of tenofovir alafenamide in the body may be affected by the activity of OATP1B1 and OATP1B3. Pregnancy & lactation: Use in pregnancy only if potential benefit justifies the potential risk to the foetus. Breast-feeding: not recommended. Side effects: Refer to SPC for full information regarding side effects. Very common (≥1/10): Nausea. Common (≥1/100 to <1/10): Headache, dizziness, diarrhoea, vomiting, abdominal pain, flatulence, abnormal dreams, rash & fatigue. Uncommon (≥1/1000 to <1/100): anaemia, arthralgia, dyspepsia, angioedema & pruritus. Legal Category: POM. Pack: Bottle of 30 film-coated tablets. Price: UK NHS List Price - £355.73; Eire/Ireland – POA. Marketing Authorisation Number: EU/1/16/1099/001; EU/1/16/1099/003.

Further information is available from Gilead Sciences Ltd, 280 High Holborn, London, WC1V 7EE, UK; Telephone: +44 (0) 8000 113700, For Ireland: +353 214 825 999. E-mail: ukmedinfo@gilead.com. Descovy is a trademark. Date of approval: April 2017; DVY/UK/17-04/MMAR/1100

▼This medicinal product is currently subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse reactions to Descovy should be reported to Gilead via email to Safety_FC@gilead.com or by telephone +44 (0) 1223 897500.

Adverse events should be reported. For the UK, reporting forms and information can be found at www.yellowcard.mhra.gov.uk

For Ireland, suspected adverse reactions should be reported to the HPRA Pharmacovigilance using a Yellow Card obtained either from the HPRA, or electronically via the website at www.hpra.ie. Adverse reactions can also be reported to the HPRA by calling +353 1 6764971.
Prescribing information for Genvoya

Consult the Summary of Product Characteristics before prescribing. GENVOOYA® elvitegravir 150mg/cobicistat 150mg/emtricitabine 200mg/ tenofovir alafenamide 10mg film coated tablets.

Indication: Treatment of HIV-1 infection in adults & adolescents (aged 12 years & older weighing at least 35 kg) without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir. Dosage: Adults & adolescents (aged ≥ 12 years, weighing at least 35 kg): One tablet, once daily, orally & whole with food. Children (< 12 years or weighing < 35kg): Safety & efficacy has not been established. Elderly: No dose adjustment is required. Renal: No dose adjustment is required in adult or adolescent patients (aged ≥ 12 years, weighing at least 35 kg) with estimated creatinine clearance (CrCl) ≥ 30 mL/min. In patients with CrCl < 30 mL/min: not recommended. Should be discontinued in patients whose CrCl declines to < 30 mL/min during treatment. Hepatic: Mild/moderate hepatic impairment: no dose adjustment required. Severe hepatic impairment: not recommended. Contraindications: Hypersensitivity to the active substances or to any excipients. Coadministration with alfuzosin, amiodarone, quinidine, carbamazepine, phenobarbital, phenytoin, rifampicin, dihydroergotamine, ergometrine, ergotamine, cisapride, St. John’s wort, lovastatin, simvastatin, pimozide, sildenafil for treatment of pulmonary arterial hypertension & oral midazolam & triazolam. Warnings & Precautions: Should not be co-administered with other antiretroviral products. Safety & efficacy in HBV/HCV co-infection has not been established. Co-infected HIV/HBV patients should be closely monitored for at least several months following discontinuation for symptoms of severe acute exacerbations of hepatitis. Should not be administered concomitantly with medicines containing tenofovir disoproxil fumarate or adefovir for treatment of HBV infection. Patients with galactose intolerance, Lapp lactase deficiency & glucose-galactose malabsorption should not take Genvoya. Women of childbearing potential should use either a hormonal contraceptive containing at least 30 μg ethinylestradiol & norgestimate as the progestagen or an alternative reliable method of contraception. Risks of mitochondrial dysfunction, immune reactivation syndrome, opportunistic infections, osteonecrosis with nucleoside analogues & CART therapy. Interactions: Co-administration with medicines that induce/inhibit CYP3A may affect the exposure of elvitegravir by decreasing its plasma concentrations leading to a reduced therapeutic effect of Genvoya. Cobicistat is an inhibitor of CYP3A & is a CYP3A substrate. Medicines highly dependent on CYP3A metabolism & have high first pass metabolism are most susceptible to large increases in exposure when co-administered with cobicistat. Medicines that inhibit CYP3A may decrease the clearance of cobicistat, resulting in increased plasma concentrations of cobicistat. Co-administration with medicines that are substrates of P-gp, BCRP, OATP1B1 & OATP1B3 may result in increased plasma concentrations of these products. Medicines that decrease renal function may increase concentrations of emtricitabine. Pregnancy & lactation: Should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. It should not be used during breast-feeding. Side effects: Refer to SPC for full information regarding side effects. Very common (≥1/10): Nausea. Common (≥1/100 to <1/10): Headache, dizziness, diarrhoea, vomiting, abdominal pain, flatulence, abnormal dreams, rash & fatigue. Uncommon (≥1/1000 to <1/100): anaemia, depression, dyspepsia, angioedema & purpura. Legal Category: POM. Pack: Bottle of 30 film-coated tablets. Price: UK NHS List Price - £879.51; Éire/Ireland – POA. Marketing Authorisation Number: EU/1/15/1061/001

Further information is available from Gilead Sciences Ltd, 280 High Holborn, London, WC1V 7EE, UK; Telephone: +44 (0) 8000 113700. E-mail: ukmedinfo@gilead.com. Genvoya is a trademark. Date of approval: April 2017. Job Bag No: GNV/UK/17-04/MMAR/1118

▼This medicinal product is currently subject to additional monitoring.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse reactions to Genvoya should be reported to Gilead via email to safety_FC@gilead.com or by telephone +44 (0) 1223 897500.

Adverse events should be reported. For the UK, reporting forms and information can be found at www.mhra.gov.uk/yellowcard

For Ireland, suspected adverse reactions should be reported to the HPRA Pharmacovigilance using a Yellow Card obtained either from the HPRA, or electronically via the website at www.hpra.ie. Adverse reactions can also be reported to the HPRA by calling +353 1 6764971.
Prescribing information for Odefsey

Consult the Summary of Product Characteristics (SPC) before prescribing.

Odefsey® ▼ emtricitabine 200mg/ rilpivirine 25mg/ tenofovir alafenamide 25mg film coated tablets.

**Indication:** Treatment of HIV-1 infection in adults & adolescents (aged ≥ 12 years & older weighing at least 35 kg) without any known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor class, tenofovir or emtricitabine and with a viral load ≤ 100,000 HIV-1 RNA copies/mL. Dosage: Adults & adolescents (aged ≥ 12 years, weighing at least 35 kg): One tablet, once daily, orally with food. Children (< 12 years of age or weighing < 35 kg): Safety & efficacy has not been established. Elderly: No dose adjustment is required. Renal: No dose adjustment is required in adult or adolescent patients (aged ≥ 12 years, weighing at least 35 kg) with estimated creatinine clearance (CrCl) ≥ 30 mL/min. In patients with CrCl < 30 mL/min: not recommended. Should be discontinued in patients whose CrCl declines to < 30 mL/min during treatment. Hepatic: Mild/moderate hepatic impairment: no dose adjustment required. Use with caution in patients with moderate hepatic impairment. Severe hepatic impairment: not recommended. Contraindications: Hypersensitivity to the active substances or to any excipients. It should not be co-administered with medicines that can result in significant decreases in rilpivirine plasma concentrations (due to cytochrome P450 [CYP3A] enzyme induction or gastric pH increase), which may result in loss of therapeutic effect of Odefsey including: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampicin, rifapentine, omeprazole, esomeprazole, dexamethasone (oral and parenteral doses), except as a single dose treatment, St. John’s wort. Warnings & Precautions: There are insufficient data to justify the use in patients with prior NNRTI failure. Resistance testing and/or historical resistance data should guide the use of Odefsey. At supratherapeutic doses (75 mg once daily and 300 mg once daily), rilpivirine has been associated with prolongation of the QTc interval of the electrocardiogram (ECG). Should be used with caution when co-administered with medicines with a known risk of torsade de Pointes. Safety & efficacy in HBV or HCV co-infection has not been established. Co-infected HIV/HBV subjects should be closely monitored with both clinical and laboratory follow up for at least several months following discontinuation for symptoms of severe acute exacerbations of hepatitis. The safety and efficacy of Odefsey in patients with significant underlying liver disorders have not been established. Risks of mitochondrial dysfunction, immune reactivation syndrome, opportunistic infections, osteonecrosis with CART therapy. Should not be co-administered with other antiretroviral medicines or with other medicines containing tenofovir alafenamide, lamivudine, tenofovir disoproxil or adefovir dipivoxil. Interactions: Co-administration of emtricitabine with medicines that are eliminated by active tubular secretion may increase concentrations of emtricitabine and/or the co-administered medicines. Medicines that decrease renal function may increase concentrations of emtricitabine. Rilpivirine is primarily metabolised by CYP3A. Medicines that induce or inhibit CYP3A may thus affect the clearance of rilpivirine. Medicines that induce P-glycoprotein (P-gp) are expected to decrease the absorption of tenofovir alafenamide, resulting in decreased plasma concentration of tenofovir alafenamide, which may lead to a loss of therapeutic effect of Odefsey and development of resistance. Co-administration with medicines that inhibit P-gp are expected to increase the absorption and plasma concentration of tenofovir alafenamide. Tenofovir alafenamide is a substrate of OATP1B1 and OATP1B3 in vitro. The distribution of tenofovir alafenamide in the body may be affected by the activity of OATP1B1 and OATP1B3. Pregnancy & lactation: Use in pregnancy only if potential benefit justifies the potential risk to the foetus. Breast-feeding: not recommended. Side effects: Refer to SPC for full information regarding side effects. Very common (≥1/10): increased total cholesterol (fasted), increased LDL cholesterol (fasted), insomnia, headache, dizziness, nausea, increased pancreatic amylase, increased transaminases (AST and/or ALT). Common (≥1/100 to <1/10): decreased white blood cell count, decreased haemoglobin, decreased platelet count, decreased appetite, increased triglycerides (fasted), depression, abnormal dreams, sleep disorders, depressed mood, somnolence, abdominal pain, vomiting, increased lipase, abdominal discomfort, dry mouth, flatulence, diarrhoea, increased bilirubin, rash, fatigue. Uncommon (≥1/1000 to <1/100): anaemia, immune reactivation syndrome, dyspepsia, severe skin reactions with systemic symptoms, angioedema, pruritus, arthralgia. Legal Category: POM. Pack: Bottle of 30 film-coated tablets. Price: UK NHS List Price - £525.95, Eire/Ireland – POA. Marketing Authorisation Number: EU/1/16/1112/001; EU/1/16/1112/002.

Further information is available from Gilead Sciences Ltd, 280 High Holborn, London, WC1V 7EE, UK; Telephone: +44 (0) 8000 113700, For Ireland: +353 214 825 999. E-mail: ukmedinfo@gilead.com. Odefsey is a trademark. Date of approval: March 2017; ODE/UK/17-03/MMAR/1024

▼ This medicinal product is currently subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse reactions to Odefsey should be reported to Gilead via email to Safety_FC@gilead.com or by telephone +44 (0) 1223 897500.

Adverse events should be reported. For the UK, reporting forms and information can be found at [www.yellowcard.mhra.gov.uk](http://www.yellowcard.mhra.gov.uk)

For Ireland, suspected adverse reactions should be reported to the HPRA Pharmacovigilance using a Yellow Card obtained either from the HPRA, or electronically via the website at www.hpra.ie. Adverse reactions can also be reported to the HPRA by calling +353 1 6764971.