New antiretroviral drugs on the horizon

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With grateful thanks to Dr Caroline Foster, Dr Steve Welch and Polly Clayden
Zidovudine (AZT) in 1987
Antiretroviral choices in 2016
### UK Antiretrovirals 2016

#### NRTIs
- **Lamivudine**
  - *Combination*: Kivexa, Triumeq, Combivir & Trizivir
- **Abacavir**
  - *Combination*: Kivexa, Triumeq & Trizivir
- **Tenofovir DF**
  - *Combination*: Truvada, Atripla, Eviplera & Stribild
- **Tenofovir AF**
  - *Combination*: Descovy, Genvoya, Odefsey
- **Emtricitabine**
  - *Combination*: Truvada, Descovy, Atripla, Eviplera, Odefsey & Stribild
- **Zidovudine**
  - *Combination*: Combivir & Trizivir

#### NNRTIs
- **Efavirenz**
  - *Combination*: Atripla
- **Nevirapine**
- **Etravirine**
- **Rilpivirine**
  - *Combination*: Eviplera, Odefsey

#### PIs
- **Lopinavir**
  - *Combination*: Kaletra
- **Atazanavir**
- **Darunavir**
  - *Combination*: Rezolsta

#### Boosters
- **Ritonavir** (low dose)
  - *Combination*: Kaletra
- **Cobicistat**
  - *Combination*: Evotaz, Rezolsta, Stribild, Genvoya

#### Integrase Inhibitors
- **Raltegravir**
- **Elvitegravir**
  - *Combination*: Stribild, Genvoya
- **Dolutegravir**
  - *Combination*: Triumeq

#### CCR5 Entry Inhibitor
- **Maraviroc**
What is new in 2016?

- New medicines
- New uses for old(er) medicines
- New formulations
- New “Fixed Dose Combination” (FDC) tablets
- New commissioning arrangements
- New guidelines
  - Local, national, international
- New generic products

Building healthier lives

Heart of England
NHS Foundation Trust
Age of UK/Irish cohort of patients with HIV acquired in childhood & seen in paediatric care, 1996-2014

Note: Data are for all children and young people alive who were ever in follow-up from 1996 onwards, including children who have since transferred to adult care; those who subsequently died or were lost to follow-up or transferred to adult care are excluded from the year of death or loss to follow-up or transfer. All paediatric infections are included, regardless of mode of acquisition (94% perinatal). CHIPS includes all diagnosed HIV-infected children known to be living in the UK/Ireland, of whom ~50% were born abroad. Data for 2014 are incomplete as subject to reporting delay.
What are the “newer” antiretroviral drugs?
Newer antiretroviral drugs

- **Protease inhibitors** (including boosters)
  - Rilpivirine *(Eviplera)*
  - Cobicistat *(Stribild, Rezolsta, Evotaz & Genvoya)*
  - Elvitegravir *(Stribild, Genvoya)*
  - Dolutegravir *(Tivicay & Triumeq)*
- **Tenofovir Alafenamide Fumarate** [TAF]
  *(Descovy, Genvoya, Odefsey)*
Protease Inhibitors (PIs)

- **Lopinavir** (*Kaletra*)
  - Twice a day
  - Paediatric tablets, liquid
  - FDA pellets, Cipla granules (& FDC)

- **Atazanavir** (*Reyataz & Evotaz*)
  - Once a day

- **Darunavir** (*Prezista & Rezolsta*)

Better lipid profiles with once daily PIs
Choice of PI for adolescents

Darunavir  
Atazanavir  
Kaletra

800mg  
300mg
Protease inhibitor boosters

Ritonavir (*Norvir*)

- Liquid discontinued
- New powder for oral suspension formulation – 100mg sachets (x 30)
- 10mg/ml – in water, chocolate milk, infant formula or used as a sprinkle on soft food
- No alcohol
- No polyethylene glycol
- Cheaper (~£35), longer shelf-life (3 years)
Cobicistat (Tybost)

- Potent CYP3A inhibitor with no antiviral activity
- Similar effect on lipid profiles to ritonavir
- Inhibits tubular secretion of creatinine and increases serum creatinine
- Reduces estimated GFR but not true GFR
- Approved in 2014, FDCs in 2015
- Dose 150mg
- In development: 50mg tablets and 20mg dispersible tablets for oral suspension
**Rezolsta**: Darunavir/cobicistat

**Evotaz**: Atazanavir/cobicistat

- **Rezolsta**: 2014 EMA approval in adults 18+
- **Evotaz**: July 2015 EMA approved in adults 18+
  - (NB: NHS England, SIGN, AWMSG)
- Current dose-finding PK study: treatment-experienced children (suppressed VL) aged 3 months to 18 years - switch from ritonavir to cobicistat to confirm the dose
- Reduced-dose co-formulations planned
Darunavir – what’s new?

Tablets and Oral suspension

- **Once** a day (+ booster) + backbone
  - antiretroviral naïve patients
  - antiretroviral experienced (no darunavir resistance, VL < 100,000 and CD4 ≥ 100)
- **Twice** a day (+ booster) with food + backbone
  - PI resistance

Oral suspension available 100mg/ml x 200ml bottle

*Darunavir 240mg/ritonavir 40mg combination tablet for ≥ 10kg – twice daily dosing (WHO priority)*
Darunavir side effects

- **Rash** (7%)/ SJS (<0.5%) – do not use/caution if sulphonamide moiety allergy – *e.g.* co-trimoxazole (*Septrin*), dapsone, (+ some diuretics, oral diabetic meds, anticonvulsants)
  - risk of rash increased with raltegravir
  - adults: 0.5% discontinued due to rash

- **Hepatitis** (0.5%) – check liver function at 2 weeks and 4 weeks after starting
**Tenofovir – what’s new?**

**Tenofovir Alafenamide Fumarate (TAF)**

- Tenofovir pro-drug
- Lower plasma tenofovir levels than TDF
- Better safety profile in adults (renal and bone) – yet to be confirmed in children
- 25mg daily with no booster, or 10mg daily
- Available as combination tablets:

  *Descovy (FTC/TAF)* 10mg and 25mg dose
  *Genvoya* (Elvitegravir/cobicistat/emtricitabine/TAF 10mg)
  *Odefsey* (emtricitabine, rilpivirine, TAF 25mg)
# TAF FDCs – approval via the MDT

<table>
<thead>
<tr>
<th>Product</th>
<th>Description</th>
<th>Formula</th>
<th>Approval Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emtricitabine / Tenofovir alafenamide</td>
<td>Emtricitabine 200mg + either: 10mg TAF with booster or 25 mg TAF without booster</td>
<td>F/TAF</td>
<td>Descovy</td>
</tr>
<tr>
<td>Emtricitabine / Tenofovir alafenamide</td>
<td>Emtricitabine 200mg TAF 25mg Rilpivirine 25mg</td>
<td>F/TAF/RPV</td>
<td>Odefsey</td>
</tr>
<tr>
<td>Elvitegravir / Cobicistat / emtricitabine/ Tenofovir alafenamide</td>
<td>Elvitegravir 150mg Cobicistat 150mg Emtricitabine 200mg TAF 10mg</td>
<td>E/c/F/TAF</td>
<td>Genvoya</td>
</tr>
</tbody>
</table>
TAF: Tenofovir alafenamide

TAF – A Novel Prodrug of Tenofovir

- **GI TRACT**: Dianion
  - **TFV** (tenofovir)
  - **TDF** (tenofovir disoproxil fumarate) 300 mg
  - **TAF** (tenofovir alafenamide) 25 mg

- **RENAL TUBULAR CELL**
  - **OAT 1 & 3**
  - **TFV**

- **PLASMA**
  - **SHORT PLASMA HALF-LIFE**
  - **LONGER PLASMA HALF-LIFE** - GREATER PLASMA STABILITY
  - >90% LESS PLASMA TFV

- **LYMPHOCYTE**
  - **TFV**

- **HIV**

*TFV based on in vitro plasma data - TDF = 0.4 minutes, TAF = 90 minutes.
TAF and adolescents

**F/TAF**

- > 6 years: switch study (GS-US-311-1269) v. FTC/TDF
  - 12 – 18 years switched first (PK study) then 6 – 12 years
- 4 weeks – 6 years study planned – reduced-dose tablets and “non-solid” formulation in development (bitter taste)

**E/C/F/TAF**

- 292-0106 study
  - Treatment naive
  - 12 – 17 year olds
  - Open label E/C/F/TAF
  - Effective, well tolerated, PK similar to adults
  - CROI 2016: Abstract 817

- 6 – 12 years study ongoing
Paediatric tenofovir DF

**Child powder dosing:** (2 – 12yrs) 8mg/kg OD; 1 scoop = 40mg; (10-12kg) → 2 scoops (scp), (12-14kg) → 2.5 scp, (14-17kg) → 3 scp, (17-19kg) → 3.5 scp, (19-22kg) → 4 scp, (22-24kg) → 4.5 scp, (24-27kg) → 5 scp, (27-29kg) → 5.5 scp, (29-32kg) → 6 scp, (32-34kg) → 6.5 scp, (34-35kg) → 7 scp, (≥35kg) 7.5 scp.

**Paed tab dosing:** (17-22kg): 150mg OD, (23-28kg) 200mg OD, (28-34kg) 250mg OD, (≥35kg): 300mg OD

All doses based on Tenofovir Disoproxil Fumarate.

Headache, nausea, vomiting, renal tubular dysfunction, bone demineralization, exacerbations of hepatitis on discontinuation. **Important:** Renal function, blood and urine monitoring. Consider TDM.

<table>
<thead>
<tr>
<th>Body Weight Kilogram (kg)</th>
<th>Oral Powder Once Daily Scoops of Powder</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 to 12</td>
<td>2</td>
</tr>
<tr>
<td>12 to 14</td>
<td>2.5</td>
</tr>
<tr>
<td>14 to 17</td>
<td>3</td>
</tr>
<tr>
<td>17 to 19</td>
<td>3.5</td>
</tr>
<tr>
<td>19 to 22</td>
<td>4</td>
</tr>
<tr>
<td>22 to 24</td>
<td>4.5</td>
</tr>
<tr>
<td>24 to 27</td>
<td>5</td>
</tr>
<tr>
<td>27 to 29</td>
<td>5.5</td>
</tr>
<tr>
<td>29 to 32</td>
<td>6</td>
</tr>
<tr>
<td>32 to 34</td>
<td>6.5</td>
</tr>
<tr>
<td>34 to 35</td>
<td>7</td>
</tr>
<tr>
<td>≥35</td>
<td>7.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Body Weight Kilogram (kg)</th>
<th>Tablets Once Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 to &lt;22</td>
<td>150 mg</td>
</tr>
<tr>
<td>22 to &lt;28</td>
<td>200 mg</td>
</tr>
<tr>
<td>28 to &lt;35</td>
<td>250 mg</td>
</tr>
<tr>
<td>≥35</td>
<td>300 mg</td>
</tr>
</tbody>
</table>
TDF monitoring

- Boosted atazanavir, darunavir, lopinavir all increase tenofovir concentrations (monitor)
- Unboosted atazanavir reduced by tenofovir – use booster
- Renal – proximal tubular leak: urine dip or urine protein/creatinine ratio every OPD
- Bone Mineral Density – consider with steroids, injectable contraceptives
**Stribild / Genvoya**

Elvitegravir 150mg  
+ Cobicistat 150mg  
+ Emtricitabine 200mg  
+ Tenofovir disoproxil 245mg or tenofovir alafenamide 10mg

- 1 tablet once a day with food  
- ≥ 18 years of age  
- ART naive or ART experienced  
- In development  
  - Reduced dose tablets for 6 – 11 year olds  
  - Adolescent study (236-0112) 12 – 17 year olds
Etravirine

Current use

- Licensed > 6 years of age (≥ 16kg)
- Treatment experienced
- 5.2mg/kg twice a day – dose banding table
- Twice daily dose (scored 25mg, 100mg & 200mg tablets available)

Paediatric studies

- P1090 study
- 2 months - 6 years of age
- Treatment naive and treatment-experienced
Rilpivirine

*Edurant* 25mg tablets
- antiretroviral treatment-naïve adult patients with a viral load ≤ 100,000
- 25mg daily + backbone WITH FOOD

PAINT study
- open-label, PK, naive adolescents <12 – >18 years – 25mg daily plus backbone
- Submitted to FDA

IMPAACT P111
- 2 weeks – 12 years

Planned formulations
- Sprinkle /granule (2.5mg/g)
Integrase Inhibitors

- Dolutegravir, raltegravir, elvitegravir
- Change in CHIVA PEP guidelines

Viral DNA is transported through the nuclear pore and integrated into host chromosomal DNA made possible by the action of virally-derived integrase. The integrated form of viral DNA is known as a provirus.
Raltegravir

Late breaker:
Once daily preparation (2 x 600mg tablets) being studied
### Post-Exposure Prophylaxis (PEP) Guidelines for children and adolescents potentially exposed to blood-borne viruses

**Authors:** C Foster, G Tudor-Williams, A Bamford

**Date reviewed:** June 2015

<table>
<thead>
<tr>
<th>Age</th>
<th>Preferred PEP</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>10+ (≥ 35kg)</td>
<td><strong>Raltegravir</strong> + <strong>Truvada</strong></td>
<td>1. <strong>Raltegravir</strong> + <strong>Combivir</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Kaletra® + <strong>Combivir</strong></td>
</tr>
<tr>
<td>6-9 years</td>
<td><strong>Raltegravir</strong> + lamivudine + zidovudine</td>
<td>1. Kaletra® + lamivudine + zidovudine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. <strong>Raltegravir</strong> or Kaletra® + lamivudine + paed TDF</td>
</tr>
<tr>
<td>2-&lt;6 years</td>
<td>Kaletra® + lamivudine + zidovudine</td>
<td>1. <strong>Raltegravir</strong> + lamivudine + zidovudine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. <strong>Raltegravir</strong> or Kaletra® + lamivudine + paed TDF</td>
</tr>
<tr>
<td>&lt; 2 years</td>
<td>Kaletra® + lamivudine + zidovudine</td>
<td></td>
</tr>
</tbody>
</table>
Raltegravir – paediatrics

- Paediatric licence (“adults, adolescents, children, toddlers and infants from the age of 4 weeks”)

- 25mg, 100mg chewable tablets
  - Maximum dose of chewable tablets = **300mg** twice a day – NOT bioequivalent

- 100mg granules for oral suspension (20mg/ml)
  - 6 mg/kg/dose twice daily

- 400mg tablets
  - Age ≥ 6 years

- Raltegravir metabolic pathway (UGT1A1) immature at birth and changes rapidly – reaches adult levels at age 3 – 6 months of age
Raltegravir in neonates

- Raltegravir crosses the placenta well
- Preventing mother-to-child transmission (P1097 Study)
  - Mothers ≥ 2 weeks raltegravir 400mg BD prior to birth
  - Cord blood & maternal blood level sampling
  - Blood samples from neonates
  - Mean neonatal half-life was 23.2 hours (range: 9.3–87.8 hours). No safety issues were identified at 20 weeks of life from in utero and transplacental exposure.
- Now looking at low birth weight/preterm infants
Raltegravir P1110 study

- Neonatal dosing study – dosing for neonates & infants ≤ 6 weeks
- **Cohort 1**: Two doses (3mg/kg): at birth and at 7 – 10 days (in addition to SOC).
  - Doses adjusted as study progressed – reduced to 2mg/kg
  - Raltegravir-exposed infants excluded then added: 1.5mg/kg
- **Cohort 2**: raltegravir-naïve neonates
- Multiple doses: at birth and up to six weeks of age
  - 1.5mg/kg daily for 7 days, then 3mg/kg twice a day until 4 weeks, then 6mg/kg twice a day
- Random raltegravir levels
Dolutegravir

- EMA licensing from 12 years/40kg
- 50mg tablet
- *Triumeq*: combined FDC with *Kivexa*
- S/E rash, SJS, hepatitis, insomnia, headache, mood disturbance

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**DOSAGE AND ADMINISTRATION**

May be taken without regard to meals. (2)

<table>
<thead>
<tr>
<th>Adult Population</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naïve or treatment-experienced INSTI-naïve</td>
<td>50 mg once daily</td>
</tr>
<tr>
<td>Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with the following potent UGT1A/CYP3A inducers: efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin</td>
<td>50 mg twice daily</td>
</tr>
<tr>
<td>INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance(12.4)</td>
<td>50 mg twice daily</td>
</tr>
</tbody>
</table>

*Alternative combinations that do not include metabolic inducers should be considered where possible.*
Triumeq

- Licensed from 12 years/ 40kg
- HLA B5701 test (as abacavir)
- Includes VL >100,000 c/ml
- Single tablet regimen but large tablet
- Very rapid fall in VL
- Recent concerns re mood disturbance, insomnia
- No integrase resistance yet documented in treatment naïve patients
- Paediatric formulation in development
Integrase Inhibitor usage in paediatrics: a single centre cohort experience

E Refsum NE Mackie S Kaye EGH Lyall G Tudor-Williams C Foster, BHIVA & CHIVA 2016

- Single centre audit; 19 children received INSTI-based ART
- 58% female, 90% Black African
- Median age 15.1 years (r 2.2 - 17.5)
- Median weight 58.6 kg (r 14.1-117.4 kg)
- **Raltegravir (9)**: 7/9 children VL <20 copies/ml after a median of 52 days, 5 discontinued RAL: rash (1), neutropenia (1), planned simplification (1), switch to once daily DTG (2)
- **Dolutegravir (10)**: Of the 4 children with detectable viraemia median time to VL suppression was 22 days. All 10 remain suppressed at a median of 24 weeks of DTG
Dolutegravir – paediatric plans

- 6-12 years FDA approved
- IMPAACT 1093

Table A – Film-Coated Tablets – dose of ~1 mg/kg with maximum dose of 50 mg

<table>
<thead>
<tr>
<th>Weight Band (kg)</th>
<th>Dose (mg)</th>
<th>Film-coated tablets taken</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 -&lt; 20</td>
<td>20</td>
<td>Two 10 mg tablets</td>
<td>1.33</td>
</tr>
<tr>
<td>20 -&lt; 30</td>
<td>25</td>
<td>One 25 mg tablet</td>
<td>1.25</td>
</tr>
<tr>
<td>30 -&lt; 40</td>
<td>35</td>
<td>One 10 mg tablet AND one 25 mg tablet</td>
<td>1.17</td>
</tr>
<tr>
<td>≥ 40</td>
<td>50</td>
<td>One 50 mg tablet*</td>
<td>1.25</td>
</tr>
</tbody>
</table>

*The 50 mg dose can consist of either ONE 50 mg tablet or TWO 25 mg tablets

- 4 weeks – 6 years on going (?May 2018)
- 1mg/kg dose
- 5mg dispersible tablets (strawberry cream flavour) and granule formulation in development
ODYSSEY (PENTA 20): A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line ART.

700 eligible children aged <18 yrs starting first-line or second-line ART

First-line ART
ODYSSEY A
310 patients
Randomise 1:1

DTG ARM
Dolutegravir + 2 NRTIs
155 patients

SOC ARM
bPI/NNRTI + 2/3 NRTIs
155 patients

Second-line ART
ODYSSEY B
390 patients
Randomise 1:1

DTG ARM
Dolutegravir + 2 NRTIs
195 patients

SOC ARM
bPI/NNRTI/RAL + 2 NRTIs
195 patients

Follow-up
until the last patient reaches 96 weeks
New drugs in development

• **Cabotegravir:**
  - Long-acting IM injectable formulation with rilpivirine
  - “age-appropriate” liquid formulation for induction in development (2 – 18 year olds)
  - LATTE-2 study: first ever long-acting (LA) injectable HIV treatment regimen
    - 20 week induction with oral meds – cabotegravir 30mg + lamivudine/abacavir + rilpivirine 25mg for last 4 weeks
    - 4-weekly or 8-weekly injections of cabotegravir/rilpivirine v. oral
    - Injectable cabotegravir and rilpivirine were generally safe and well-tolerated. Serious adverse events occurred in 6% of people who switched to the long-acting injectables and 5% of those who stayed on the oral regimen, but these were not considered drug-related
    - Study participants reported a high level of satisfaction with their treatment – more than 90% receiving the long-acting injections reported that they were satisfied, compared with about 70% of those on the oral regimen.

• **Doravirine**
  - New NNRTI (Merck MK-1439)
  - Phase 2 results (+ Truvada v. efavirenz)
  - FDC planned: doravirine/tenofovir DF/lamivudine
LATTE-2 Study: switch to cabotegravir LA + rilpivirine LA IM

- LATTE-2 results successfully demonstrate ability to maintain HIV-1 RNA < 50 c/mL with IM CAB + RPV LA, dosed every 4 or 8 weeks
- Injection tolerability
  - Majority of injection site reactions (ISR) were grade 1 to 2 pain, with a median duration of 3 days
  - Few subjects had an ISR that led to discontinuation
  - High overall reported satisfaction
- Dose selection
  - 4-weekly dosing resulted in lower rates of virologic non-response with similar safety to dosing every 8 weeks
  - 4-weekly dosing was selected for pivotal phase III studies
  - 8-weekly dosing remains under evaluation within LATTE-2
The arrival of generic ARVs in the UK

- A **generic drug** is a medicine defined as "a drug product that is comparable to brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use".

- Although they may not be associated with a particular company, generic drugs are subject to the regulations of the governments of countries where they are dispensed.

- Generic drugs are labelled with the name of the manufacturer and the adopted name (non-proprietary name) of the drug.

- A generic drug must contain the same active ingredients as the original formulation.
Patent Expiry Dates

2005 - 2007
- Zidovudine
- Enfurvitide
- Didanosine

2011
- Lamivudine
- Saquinavir
- Stavudine

2013
- Zidovudine + lamivudine
- Nevirapine
- Efavirenz

2014
- Abacavir

2015
- Lopinavir
- Ritonavir

2016
- Abacavir + lamivudine
- Lopinavir + ritonavir
- Emtricitabine

2018
- Atripla
- Darunavir
UK Generic ARVs

Zidovudine
- 250mg and 100mg capsules

Lamivudine
- 100mg, 150mg and 300mg tablets
- “Combivir” tablets
  - zidovudine 300mg + lamivudine 150mg

Nevirapine
- 200mg tablets, 400mg SR tablets

Efavirenz
- 600mg tablets

“Kivexa” tablets – 1st December 2016

BUT NOT ORAL LIQUID PREPARATIONS (yet....)
Lamivudine

Lamivudine 100mg tablets

Lamivudine 150mg tablets

Lamivudine 10mg/ml oral solution

Lamivudine 300mg tablets
Thank you

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With grateful thanks to Dr Caroline Foster, Dr Steve Welch and Polly Clayden