Why do we need ARV surveillance studies?

Michelle Moorhouse
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Thanks: Andy Hill, Polly Clayden
Disclosures

- Speaker fees and honoraria from Gilead Sciences, AbbVie, Cipla, Mylan, Aspen, Sanofi, Pfizer and Janssen
- Conference sponsorship from BD, Gilead, Janssen, Merck, Cipla and Mylan
- Part of ART optimisation collaborations
- Funding from USAID, Unitaid, SAMRC and study drug donations from ViiV Healthcare and Gilead Sciences for ART optimisation studies
Stages of drug development

- **Development time**: Year 1-4 (including preclinical) → Year 4-7 → Year 7-9 → Year 9-11 → Year 11-12 → ongoing
- **Number of research subjects in each phase**: 10-15 → 20 - 80 → 100–300 → 1,000–3,000 → many thousands
- **Total cost**: £500 million (including preclinical) → £700 million → £900 million → £1.1 billion → £1.2 billion
- **Candidate molecules**: 10-20 → 5-10 → 2-5 → 1-2 → 1

12 years

20 molecules → 1

GBP 4.4 billion
## Stages of drug development

<table>
<thead>
<tr>
<th>Development time</th>
<th>Translational and Phase 0</th>
<th>Year 1-4 (including preclinical)</th>
<th>Year 4-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of research subjects in each phase</td>
<td>10-15</td>
<td>20 - 80</td>
<td></td>
</tr>
<tr>
<td>Total cost¹</td>
<td>£500 million (including preclinical)</td>
<td>£700 million</td>
<td></td>
</tr>
<tr>
<td>Candidate molecules</td>
<td>10-20</td>
<td>5-10</td>
<td></td>
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</tbody>
</table>
Stages of drug development

<table>
<thead>
<tr>
<th>Development time</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development time</td>
<td>Year 7-9</td>
<td>Year 9-11</td>
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</tr>
</tbody>
</table>
Stages of drug development

- **Regulatory approval**
  - Development time: Year 11-12
  - Number of research subjects in each phase: many thousands
  - Total cost: £1.2 billion
  - Candidate molecules: 1

- **Phase 4**
A shiny new molecule...

• Registrational studies are designed to
  o optimise benefits, and
  o minimise risks/adverse events

• Subjects are selected to show these effects
Let’s look at dolutegravir registrational studies

- Randomised, non-inferiority phase 3 studies
- Primary endpoint: HIV-1 RNA < 50 copies/mL at week 48

**SPRING-2** (active controlled)
- ART-naive pts VL ≥ 1000 copies/mL (N = 822)
- DTG 50 mg QD + 2 NRTIs* (n = 411)
- RAL 400 mg BID + 2 NRTIs* (n = 411)

**SINGLE** (placebo controlled)
- ART-naive pts VL ≥ 1000 copies/mL HLA-B*5701 neg CrCl > 50 mL/min (N = 833)
- DTG 50 mg QD + ABC/3TC QD (n = 414)
- EFV/TDF/FTC QD (n = 419)

**FLAMINGO** (open label)
- ART-naive pts VL ≥ 1000 copies/mL (N = 484)
- DTG 50 mg QD + 2 NRTIs* (n = 242)
- DRV/RTV 800/100 mg QD + 2 NRTIs* (n = 242)

*Investigator-selected NRTI backbone: either TDF/FTC or ABC/3TC.
SINGLE study: DTG vs. EFV

Better tolerated than EFV (but more insomnia)

Walmsley et al. J Acquir Immune Defic Syndr 2015

Proportion of participants with HIV-1 RNA < 50 copies/mL

Week 96: 8.0% (95% CI, 2.3% to 13.8%); p=0.006
Week 114: 8.3% (95% CI, 2.0% to 14.6%); p=0.010
## SINGLE study: Safety

### Dolutegravir plus Abacavir–Lamivudine for the Treatment of HIV-1 Infection

Sharon L. Walmsley, M.D., Antonio Antela, M.D., Ph.D., Nathan Clumeck, M.D.,

<table>
<thead>
<tr>
<th>Event</th>
<th>Dolutegravir and Abacavir–Lamivudine (N=414)</th>
<th>Efavirenz–Tenofovir DF–Emtricitabine (N=419)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event leading to discontinuation of study drug†</td>
<td>10 (2)</td>
<td>42 (10)</td>
</tr>
<tr>
<td>Psychiatric disorder</td>
<td>2 (&lt;1)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Nervous system disorder</td>
<td>0</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Skin and subcutaneous-tissue disorder</td>
<td>2 (&lt;1)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>0</td>
<td>8 (2)</td>
</tr>
<tr>
<td>General disorder or administration-site condition</td>
<td>0</td>
<td>7 (2)</td>
</tr>
</tbody>
</table>
Study entry criteria: inclusion

• Screening plasma HIV-1 RNA ≥ 1000 copies/mL
• Antiretroviral-naïve (≤ 10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection)
• Ability to understand and sign a written informed consent form
• Willingness to use approved methods of contraception to avoid pregnancy (women of child bearing potential only)
• Age equal to or greater than 18 years
• A negative HLAB*5701 allele assessment
Study entry criteria: exclusion

- Women who are pregnant or breastfeeding;
- Active Center for Disease and Prevention Control (CDC) Category C disease
- Hepatic impairment
- HBV co-infection
- Anticipated need for HCV therapy during the study
- Allergy or intolerance to the study drugs or their components or drugs of their class
- Malignancy within the past 5 years
- Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of Screening
- Treatment with radiation therapy, cytotoxic chemotherapeutic agents or any immunomodulator within 28 days of Screening
- Exposure to an agent with documented activity against HIV-1 in vitro or an experimental vaccine or drug within 28 days of first dose of study medication
- Primary viral resistance in the Screening result
- Verified Grade 4 laboratory abnormality
- ALT >5 xULN
- ALT ≥ 3xULN and bilirubin ≥ 1.5xULN (with >35% direct bilirubin);
- Estimated creatinine clearance <50 mL/min
- Recent history (≤3 months) of upper or lower gastrointestinal bleed
Who’s missing?

- < 18 years
- Pregnant or breastfeeding women
- HBV coinfection
- Malignancy within last 5 years
- Recent GI bleed
- Various laboratory abnormalities
  - Liver, renal
  - Grade 4

Who is excluded?
Pregnant women in dolutegravir studies

<table>
<thead>
<tr>
<th>Name</th>
<th>Population</th>
<th>ART</th>
<th>N</th>
<th>No of women on DTG arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>SINGLE</td>
<td>ARV-naive</td>
<td>DTG + ABC/3TC vs EFV/TDF/FTC</td>
<td>144</td>
<td>67</td>
</tr>
<tr>
<td>SPRING 2</td>
<td>ARV-naive</td>
<td>2NRTI + DTG vs 2NRTI + RAL</td>
<td>822</td>
<td>63</td>
</tr>
<tr>
<td>FLAMINGO</td>
<td>ARV-naive</td>
<td>2NRTI + DTG vs 2NRTI + DRV/r</td>
<td>484</td>
<td>31</td>
</tr>
<tr>
<td>SAILING</td>
<td>Experienced</td>
<td>OB + DTG vs OB + RAL</td>
<td>719</td>
<td>107</td>
</tr>
<tr>
<td>STRIIDING</td>
<td>Switch</td>
<td>2NRTI/DTG vs current ART</td>
<td>551</td>
<td>77</td>
</tr>
<tr>
<td>SWORD 1&amp;2</td>
<td>Switch</td>
<td>RPV + DTG vs current ART</td>
<td>1024</td>
<td>120</td>
</tr>
<tr>
<td>ARIA</td>
<td>ARV-naïve women</td>
<td>DTG/ABC/3TC vs ATV/r + TDF/FTC</td>
<td>495</td>
<td>250</td>
</tr>
<tr>
<td>DAWNING</td>
<td>Experienced</td>
<td>2NRTI + DTG vs 2NRTI + LPV/r</td>
<td>627</td>
<td>116</td>
</tr>
<tr>
<td>INSPIRING</td>
<td>TB</td>
<td>2NRTI + DTG twice daily vs 2NRTI + EFV with RIF-based co-treatment</td>
<td>113</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total: 4979</td>
<td>867</td>
</tr>
</tbody>
</table>

Thanks Polly Clayden!
### Anyone else missing?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DTG 50 mg +ABC/3TC QD (n=414)</th>
<th>EFV/TDF/FTC QD (n=419)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>36 (18-68)</td>
<td>35 (18-85)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>67 (16)</td>
<td>63 (15)</td>
</tr>
<tr>
<td>African American/African Heritage, n (%)</td>
<td>98 (24)</td>
<td>99 (24)</td>
</tr>
<tr>
<td>CDC class C, n (%)</td>
<td>18 (4)</td>
<td>17 (4)</td>
</tr>
<tr>
<td>Baseline HIV-1 RNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (log10 copies/mL)</td>
<td>4.67</td>
<td>4.70</td>
</tr>
<tr>
<td>&gt; 100,000 c/mL, n (%)</td>
<td>134 (32)</td>
<td>131 (31)</td>
</tr>
<tr>
<td>Median CD4 cell count, cells/uL</td>
<td>334.5</td>
<td>339.0</td>
</tr>
<tr>
<td>&lt; 200, %</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>200 to &lt; 350, %</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td>350 to &lt; 500, %</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>≥ 500, %</td>
<td>15</td>
<td>17</td>
</tr>
</tbody>
</table>

A shiny new molecule...

• Registrational studies are designed to
  o optimise benefits, and
  o minimise risks/adverse events

• Subjects are selected to show these effects
Honeymoon phase

Drug just launched

Efficacy great

Safety profile looks good
BUT...

• Clinical trials are very different from the real world of medical practice and care
• No drug is safe and effective for everybody
• Clinical trials are needed to develop labelling instructions on how to use the drug to obtain its benefits and reduce risks of harms
• Trials are usually just large enough and long enough to support efficacy findings

1. Do they really provide full information on how to use ARVs in sicker people living with HIV?
2. Are the results generalisable to all PLWHIV?
Gaps on dolutegravir after registration

Long term tolerability in the real world

Advanced HIV disease

Comorbidity: TB HBV NCDs etc

Pregnant/BF women

Infants and children

Diverse populations

Elderly/Ageing

Drug interactions

Adapted from: Meg Doherty, WHO 2018
Marriage blues

In the long-term, new evidence emerges.....

New patient populations, larger sample sizes, new methods to study adverse events
DTG in the real world...

Dolutegravir: discontinuation due to AE
Germany (2 cohorts), 1950 INSTI-based therapies

Discontinuation due to neuropsychiatric AE

Factors associated with DTG discontinuation

<table>
<thead>
<tr>
<th>Factor</th>
<th>RH</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, vs. male gender</td>
<td>2.81</td>
<td>1.46–5.41</td>
<td>0.002</td>
</tr>
<tr>
<td>Older age (&gt; 60 years), vs. younger age</td>
<td>2.88</td>
<td>1.56–5.34</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ABC with DTG initiated, vs. no ABC</td>
<td>2.63</td>
<td>1.61–4.29</td>
<td>0.0001</td>
</tr>
<tr>
<td>DTG start in 2016, vs. in 2014/2015</td>
<td>8.93</td>
<td>3.76–21.28</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Neuropsychiatric AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, vs. male gender</td>
<td>2.64</td>
<td>1.23–5.65</td>
<td>0.01</td>
</tr>
<tr>
<td>Older age (&gt; 60 years), vs. younger age</td>
<td>2.86</td>
<td>1.42–5.77</td>
<td>0.003</td>
</tr>
<tr>
<td>ABC with DTG initiated, vs. no ABC</td>
<td>2.42</td>
<td>1.38–4.24</td>
<td>0.002</td>
</tr>
<tr>
<td>DTG start in 2016, vs. in 2014/2015</td>
<td>11.36</td>
<td>4.31–29.41</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

ABC, abacavir; CI, confidence interval.

Hoffmann et al. HIV Medicine 2017; Libre et al. CROI 2017 abstract #615;
Hsu et al. CROI 2017 abstract #664
DTG in the real world...

Hoffmann et al. HIV Medicine 2017; Libre et al. CROI 2017 abstract #615;
Hsu et al. CROI 2017 abstract #664
From CROI: Risk factors for neuropsychiatric events

Table 1: Adjusted Relative Hazards (RH) for the covariables of interest, using the Cox model.

<table>
<thead>
<tr>
<th>Risk factors for NPAEs leading to DTG discontinuation</th>
<th>RH</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, versus male gender</td>
<td>2.31</td>
<td>1.12-4.74</td>
<td>0.03</td>
</tr>
<tr>
<td>Older age (&gt; 60 years), versus younger age</td>
<td>2.14</td>
<td>1.10-4.18</td>
<td>0.025</td>
</tr>
<tr>
<td>Depressive disorders, versus no</td>
<td>1.00</td>
<td>0.54-1.88</td>
<td>0.952</td>
</tr>
<tr>
<td>Other neuropsychiatric diagnoses, versus no</td>
<td>0.93</td>
<td>0.29-3.00</td>
<td>0.896</td>
</tr>
</tbody>
</table>

Figure 3. Reasons (%) for discontinuing DTG, n=54
(mean of 2.9 symptoms/NPAEs were reported)
Weight gain?

Mean gain 3 kg
20% > 10% increase

Mean gain 5.3 kg

Significant 1-year BMI increase

76.5% gained weight
18.3% obesity

Menard A et al. AIDS, June 2017; Norwood et al, JAIDS, Aug 2017; Bakal D et al. ID Week 2017; Taramasso et al. Open Forum Infectious Diseases, Nov 2017
REAL “real” world patients on ADVANCE

- OPTIMIZE clinical trial DTG to EFV (and TAF to TDF)
- Only RCT providing a head-to-head comparison of the current standard of care
- Aligned with NIH pregnancy study

Number = 1110*
≥12 years, ≥40 kg

- Non inferiority of 2 new combinations to current treatment
- Open label, randomised, single site study over 48 weeks
- * n=1110, with 90-120 in age group 12-18 years
Dolutegravir NTD signal
Tsepamo study, Botswana

Neural tube defects in
4/426 pregnancies
(0.94%)

Updated data since 01 May 2018: 4/596 (0.67%)

95% CI still does not overlap with other groups
Detecting rare adverse events: numbers

Rare toxicities are often only seen after a drug has been approved: large numbers needed to detect rare but serious events.

<table>
<thead>
<tr>
<th>Drug-related event</th>
<th>Background risk (%)</th>
<th>Total Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attempted suicide, efavirenz (0.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-related hepatitis, darunavir (0.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe GI bleeding, aspirin (1.8%)</td>
<td></td>
<td></td>
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</tbody>
</table>

Number of patients required to detect a 100% rise in risk.
So now what?
Countries are transitioning to DTG
Should dolutegravir be given to 20 million people in low income countries?

**Pros:**
- Activity against NNRTI resistant HIV
- Well tolerated versus EFV or DRV/r
- Simple low cost co-formulation with TDF/3TC

**Cons:**
- Safety and efficacy profile mainly from Phase 3 trials in high income countries
- Safety in pregnant women and TB coinfection?
- Reports of IRIS and CNS adverse events?

Thanks Andy Hill!
The consequences of small differences in adverse event profiles

- If a drug is given to 20 million people, and there is an excess risk of 0.5% (1 in 200) for an AE such as CVD, IRIS or suicide
- This could lead to 100,000 people developing this adverse event
- So we need to be very careful when we conduct analyses of safety

Thanks Andy Hill!
Drug safety – keeping it balanced

Too cautious
- Overinterpreting trends
- Paranoia
- Scare-mongering
- New drugs not used

Too liberal
- Hiding data
- Missing important trends
- Allowing toxicity to happen
- Not updating analyses

Thanks Andy Hill!
Efavirenz controversy: conflicting evidence

Preclinical data
• NTDs in primate study

Clinical data: T1 EFV exposure
• 4 retrospective
• 1 prospective case report of NTDs in humans

Meta analysis (2011):
1 NTD
Incidence: 0.7 (95% CI 0.002 – 0.39%)
= NO association

Relative risk of birth defects: EFV vs. non-EFV regimens

We have been here before...

... more than once

Drug that appeared to be well tolerated

Toxicity issues appeared several years after the drugs were launched
The need to for ongoing, locally relevant pharmacovigilance

Pharmacovigilance: “Detection, assessment, understanding and prevention of short and long term adverse effects of medicines”

• Clinical studies short
• Comorbidities, concomitant medicines, genetic variability
• Risk versus benefit:
  • early treatment initiation
  • prevention
• Focus on serious adverse drug reactions (ADRs)
  • Resulting in hospitalisation and death
  • Treatment limiting ADRs- drug substitutions

Thanks Karen Cohen!
Spontaneous reporting

• Signal detection
  o e.g. Interstitial nephritis lopinavir/r

• ADRs that trouble HCWs
  o Guide HCW training and clinical support
  o Nurse-driven services

• Need accessible and responsive systems
  o Telephonic and online reporting in addition to paper-based
  o Prompt, individualised feedback and clinical support

• Does not give prevalence/incidence
  o No denominator; numerator quite dodgy often

Thanks Karen Cohen!

The way forward

Well powered prospective observational cohorts of sufficient duration

• Pharmacovigilance
• Identify less frequent AEs / treatment-limiting toxicities
• Enrol populations excluded from registrational studies
• Ideally in parallel to registration studies once a specified level of safety confirmed (phase 3)
  o Included as part of registrational dossiers?

Pharmacovigilance: “Detection, assessment, understanding and prevention of short and long term adverse effects of medicines”
Thanks

• Francois Venter
• Stuart Ali
• Andrew Hill
• Polly Clayden
• Karen Cohen
Michelle Moorhouse
27 Oct 2018
Southern African HIV Clinicians Society Conference