ANTI(RETRO)VIRAL DRUGS ...AND BEYOND

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Geneva University Hospitals, Switzerland
IAS plenary session, 26 July 2017
Disclosures

Unrestricted educational grants (HIV Unit, Geneva University Hospitals): MSD Merck Sharp & Dohme AG, ViiV Healthcare, Gilead Sciences SA, AbbVie, Bristol Myers Squibb

Travel Grant, February 2017: Gilead Sciences SA

Not a Patent Holder

PI of the SIMPL’HIV study (NCT03160105)

Member of the WHO HIV guidelines (2015-2016)

Member of the French ANRS committee for protocol selection (CSS6)

Member of the Swiss Federal Commission for Sexual Health (EKSG)
Contents

- The bright side of therapy
- Changes in prescription practices
- Beyond therapeutic trials
- Treatment simplification
- HIV drug pipeline
- Access issues
- What ARVs can’t do
  (cure, correct health inequities)
The bright side of therapy
Today, 19.5 million individuals worldwide receive anti HIV drugs

UNAIDS report, July 2017
53% AntiRetroviral Treatment (ART) coverage Gender and regional differences, 2016

Data source: UNAIDS report, July 2017
Thirtieth anniversary after the 1st anti HIV was commercialized
30 years of drug development (FDA approval, original)

1983
- AZT

1987
- Didanosine
- Zalcitabine
- Stavudine
- Lamivudine
- Saquinavir HG
- Saquinavir SGC
- Indinavir
- Nevirapine
- Ritonavir
- Delavirdine
- Nelfinavir
- Amprenavir
- Didanosine EC
- Lopinavir/r
- Trizivir (FDC)
- Tenofovir DF

1990 - 2002
- Rilpivirine/TDF/FTC
- Nevirapine XR
- Rilpivirine
- Elvitegravir/C/F/TDF
- Dolutegravir
- Cobicistat
- Dolutegravir/ABC/3TC
- Elvitegravir/C/F/TAF
- Darunavir/COBI
- Atazanavir/COBI
- FTC/TAF (10, 25 mg)
- Rilpivirine/TAF/FTC
- Dolutegravir

2003 -2008
- Atazanavir
- Emtricitabine
- Enfuvirtide
- Fos-APV
- Truvada (FDC)
- Tipranavir
- Atripla (FDC)
- Darunavir
- Maraviroc
- Raltegravir
- Etravirine

2011- 2016
- (submitted)
- (submitted)
- (submitted)
- (submitted)

2017-
- Raltegravir HD
- FTC/TDF
- (D/C/F/TAF)*
- (Bictegravir/TAF/C/FTC)*
- (Dolutegravir/3TC/TDF)*

- Entry inhibitors
- Integrate inhibitors (InSTI)
- Protease inhibitors (PI)
- Fusion inhibitors
- RT (non) nucleosidic inhibitors (N-NRTI)

*Generic versions

§
The dramatic impact of HIV response on life expectancy, 1950-2015

Major CHANGES in drug prescription practices
better treatment – NAIDS ambitious goals within reach

...so as to achieve containment of the HIV epidemic.

90.0% 90.0% 90.0%

Diagnosed (rapid) ART Suppressed Viral Load (<1000 cp)

In the last 10 years, 241 different initial regimens were prescribed in Switzerland. In 2016, the number of initial treatments has decreased to only 15.

90% of treatment initiation is done with 6 regimens.

Spoilt for choice
30 drugs, more than 20,000 theoretical combinations!

Wandeler et al, PLoS 2011, personal communication (Swiss HIV Cohort Study)
Currently available Once daily Fixed-Dose Combinations for treatment initiation

<table>
<thead>
<tr>
<th>ATRIPLA</th>
<th>EVI(COM)PLERA</th>
<th>STRIBILD</th>
<th>TRIUMEQ</th>
<th>GENVOYA</th>
<th>ODEFSEY</th>
</tr>
</thead>
<tbody>
<tr>
<td>DF/FTC/EFV</td>
<td>TDF/FTC/RPV</td>
<td>TDF/FTC/EVG/cob</td>
<td>DTG/ABC/3TC</td>
<td>EVG/cob/FTC/TAF</td>
<td>TAF/FTC/RPV</td>
</tr>
<tr>
<td>Take with food</td>
<td>Take with food</td>
<td>Attn: drug-drug interactions</td>
<td>Must be HLA B*5701 neg.</td>
<td>Take with food</td>
<td>Take with food</td>
</tr>
<tr>
<td>VL &lt; 100'000</td>
<td>VL &lt; 100'000</td>
<td></td>
<td></td>
<td></td>
<td>VL &lt; 100'000</td>
</tr>
</tbody>
</table>

Generic names: Atenef, Atreslawin, Atroiza, Citenvir, Heftenam, Odimune, Tribuss, Trivenz, Truno, Trustiva, Viraday

Stringent Regulatory Approval of two generic suppliers for DTG/3(F)TC/TDF expected:
Alexandra Scherrer, Swiss HIV Cohort Study, 2017

Have (the Swiss?) found the magic bullet?
Considerations for choosing a regimen: From universal access to individual treatment

<table>
<thead>
<tr>
<th>Patient-specific</th>
<th>Regimen-specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HIV-1 RNA</td>
<td>Long-term tolerability and safety</td>
</tr>
<tr>
<td>Chronic HBV or HCV coinfection</td>
<td>Simplicity</td>
</tr>
<tr>
<td>Renal function</td>
<td>Food intake requirements</td>
</tr>
<tr>
<td>Desire to become pregnant</td>
<td>ART interactions with co-medication and lifestyle drugs</td>
</tr>
<tr>
<td>Illicit drug use</td>
<td>ART genetic barrier to resistance</td>
</tr>
<tr>
<td>HLA-B*5701 status</td>
<td>Cost/Affordability</td>
</tr>
<tr>
<td>Age, Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Previous ART exposure</td>
<td></td>
</tr>
<tr>
<td>Advanced HIV disease – Acute Infection</td>
<td></td>
</tr>
</tbody>
</table>
Comparing preferred and alternative first line ART options in adults/adolescents with HIV in 2016

<table>
<thead>
<tr>
<th>GUIDELINES</th>
<th>NRTI BACKBONE</th>
<th>NNRTI</th>
<th>InSTI</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2016)</td>
<td>TAF/XTC</td>
<td>TDF/XTC</td>
<td>ABC/3TC</td>
<td>AZT/3TC</td>
</tr>
<tr>
<td>DHHS (2016)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EACS (2016)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO (2016)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>French (2017)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

preferred | alternative | not recommended/special situations

Convenient: one pill a day, minimal monitoring

Possibility of treatment harmonization (pregnant women, children, HIV-TB co-infected individuals, HIV hepatitis B co-infected individuals)

Alternative combinations

2016 WHO recommendations for first-line ART

TDF

+ 3TC (or FTC)

+ EFV$_{600}$ mg

* XTC = 3TC or FTC

TDF + XTC + DTG

TDF + XTC* + EFV$_{400}$ mg
Are we ready for the universal adoption of the WHO alternative options?

YES, with some remaining uncertainties

<table>
<thead>
<tr>
<th>ARV</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q3-Q4</td>
<td>Q1-Q2</td>
<td>Q1-Q2</td>
<td>Q1-Q2</td>
</tr>
</tbody>
</table>

DTG

- RADIO DAWNING *
- ADVANZ-4
- IMPAACT 1093
- DOLPHIN 1
- NAMSAL
- DOLPHIN 2
- D2EFT
- INSPINING
- VESTED ODYSSEY
- ADVANCE
- PANGING20

FV400

- SSAT 062 *
- SSAT 063
- NAMSAL

<table>
<thead>
<tr>
<th>Pregnant women</th>
<th>Children</th>
<th>TB</th>
<th>Adults</th>
</tr>
</thead>
</table>

* Marco Vitoria courtesy, adapted from Vitoria et al, Curr Opin HIV/AIDS, 12: 369-

- Lamorde M et al, abstract # TUPDB0203 LB, Zash R et al, #MOAX0202 LB (Botswana), Vannappagari et al, MOPEG0283 (APR)
### Positioning DTG in LMIC for naïve and experienced patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Drugs</th>
<th>Intervention</th>
<th>Major outcomes</th>
<th>N</th>
<th>Study countries</th>
<th>Expected completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAMSAL (ANRS 12313) NCT02777229</td>
<td><strong>DTG</strong> EFV&lt;sub&gt;400&lt;/sub&gt;</td>
<td>Safety/efficacy of DTG vs EFV&lt;sub&gt;400&lt;/sub&gt; TDF/3TC + DTG vs TDF/3TC + EFV&lt;sub&gt;400&lt;/sub&gt;</td>
<td>VL at 24 and 48 weeks</td>
<td>606</td>
<td>Cameroon</td>
<td>Q3 2018</td>
</tr>
<tr>
<td>NANCE (WRHI 060) NCT03122262</td>
<td><strong>DTG</strong> TAF EFV&lt;sub&gt;600&lt;/sub&gt;</td>
<td>Safety/efficacy of DTG and TAF TDF+ FTC+ DTG vs TAF + FTC + DTG vs TDF + FTC + EFV&lt;sub&gt;600&lt;/sub&gt;</td>
<td></td>
<td>1050</td>
<td>South Africa</td>
<td>Q4 2019</td>
</tr>
<tr>
<td>DAWNING (ViiV) NCT02227238</td>
<td><strong>DTG</strong> LPV/r</td>
<td>Safety/efficacy of DTG vs LPV/r in PLHIV failing first-line ART 2NRTI + DTG vs 2NRTI + LPV/r</td>
<td>VL at 96 weeks</td>
<td>612</td>
<td>Multi countries</td>
<td>Q3 2018</td>
</tr>
<tr>
<td>DAWNING (ViiV) NCT02227238</td>
<td><strong>DTG</strong></td>
<td>2NRTI + DTG vs SoC in children/young adults (6-18 yrs) with HIV starting first-line or switching to 2nd ART</td>
<td>VL at 24 and 48 weeks</td>
<td>700</td>
<td>Multi countries</td>
<td>Q3 2018</td>
</tr>
</tbody>
</table>

*78% vs. 69% <50 c/mL at week 24 Premature interruption*
Today, it is uncertain whether the most cost-effective role for DTG is to replace efavirenz as a first-line regimen, to replace boosted PIs in second-line regimens, or to replace both with a single regimen approach.
How will these new therapies position themselves in the near future?

TAG pipeline, July 2016, O’Connor J et al, the Lancet HIV, May 2017
Is TAF (tenofovir alafenamide) a candidate for inclusion in a universal regimen?

YES, with some remaining uncertainties:

- FDA validations were based on switch studies.
- No data on TAF stand-alone formulation.
- TAF data for use in children, co-administration with RIF, PreP or during pregnancy are pending.
- However, tenofovir pro-drug will dramatically reduce costs due to lower amounts of API (Active Pharmaceutical Ingredient) needed.
- Anticipated regulatory approval of generic suppliers: late 2019.
### New triple combinations for treatment initiation (phase 3)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Comparator</th>
<th>N=</th>
<th>% Women</th>
<th>Duration (week)</th>
<th>Main result</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>ABC/3TC/DTG</td>
<td>692</td>
<td>10</td>
<td>48</td>
<td>Non inferior (92.4 vs 93% &lt;50 c/mL)</td>
</tr>
<tr>
<td>3</td>
<td>TAF/FTC+DTG</td>
<td>645</td>
<td>12</td>
<td>48</td>
<td>Non inferior (89.4 vs 92.9% &lt;50 c/mL)</td>
</tr>
<tr>
<td>3</td>
<td>EFV/FTC/TDF</td>
<td>734</td>
<td>15</td>
<td>48</td>
<td>Non Inferior (84.3 vs 80.8% &lt;50 c/mL)</td>
</tr>
<tr>
<td>3</td>
<td>RAL 400 BID</td>
<td>802</td>
<td>15.4</td>
<td>96</td>
<td>Non Inferior (81.5 vs 50% &lt;40 c/mL)</td>
</tr>
</tbody>
</table>

**Not (yet) ready** for a use in a universal regimen

# MOAB0105 LB ²Abstract # TUPDB0201 LB ³Abstract # TUAB0104 LB ⁴Abstract # TULBPEB20
Beyond therapeutic trials
Therapeutic trials have a limited duration

**Therapeutic testing**
- Observational Cohorts

**Therapeutic testing**
- Observational cohorts

**AGE RANGE**

- **20** years
  - INITIATION
    - Objective
      - Reaching an undetectable viral load
  - MAINTENANCE
    - Objectives
      - Reduce drug exposure
      - Improve tolerance
      - Maintain efficiency
      - Optimize costs
      - Management of comorbidities

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From Prof Pietro Vernazza, SSI, Interlaken, 2012
Gender considerations for HIV treatment research

- Pregnancy
- Reservoir size
- Response to treatment
- Hormonal adaptation
- Drug interactions
- Contraception

Women represent less than 20% of participants in therapeutic trials.

Adapted from Jintanat Ananworanich, CROI 2017
What therapeutic trials did not show – the example of DTG’s discontinuation due to adverse events

Discontinuation due to neuropsychiatric adverse events from clinical trials

<table>
<thead>
<tr>
<th>Condition</th>
<th>SPRING-2 ART naïve – double-blind 96-week</th>
<th>FLAMINGO ART naïve open-label 96-week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>$DTG_{NRTI}$ $0$, $RAL_{NRTI}$ $0$</td>
<td>$DTG_{NRTI}$ $0$, $DRV/r_{NRTI}$ $0$</td>
</tr>
<tr>
<td>Anxiety</td>
<td>$0$, $0$</td>
<td>$0$, $0$</td>
</tr>
<tr>
<td>Depression</td>
<td>$0$, $0$</td>
<td>$0$, $0$</td>
</tr>
<tr>
<td>Suicidal thoughts</td>
<td>$0$, $2/6$</td>
<td>$1/4$, $0$</td>
</tr>
</tbody>
</table>

Log rank test, $P < 0.0001$


Feoplace A et al, Journal of Acquir Immune Acquir Immune Defic Syndr (2017); 74: 423-431,
Beyond clinical trials:
Examples of misuse of HIV antiretroviral medication

**Efavirenz** (South Africa): crushed and mixed with other ingredients, like marijuana. Teens have been reported to crush the pills and smoke the powder for its psychoactive effect.

**Zidovudine/lamivudine** (Nigeria): breast enlargement

**Ritonavir** (Miami, Florida): to prolong the effect of ecstasy, or Viagra

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Whoonga (Wunga, Zulu language)
A cocktail of drugs that many believe contains efavirenz, methamphetamine, heroin, marijuana, strychnine (?)

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Beyond clinical trials – the patient

Example: patient-reported outcomes in oncology

"The missing voice of patients in drug safety reporting"

Patient-reported outcomes improve quality of life and survival

Beyond clinical trials
Use of social media

Summary of reported toxicities by unique users on Twitter, 2010-2013

Adding a new indicator for treatment success

“Penicillin cures, but wine makes people happy”

Alexander Fleming

Make treatment light and Simple!
Strategies for Safety, tolerability and convenience

Newer approaches for short term simplified regimens

- Drug optimization (1)
  - Dose reduction

- Drug optimization (2)
  - New Formulations

- Dual Therapy:
  - Drug de-escalation

- Short cycle therapy:
  - “Week-ends” off regimens

Anna Turkova, WESY03 session, 11.20am

Christine Katlama, WESY03 session, 11.00am

BREATHER study, Butler K et al, Lancet 2016
ANRS 162-4D study, de Truchis et al AIDS 2016
THPEB063, IAS 2017 # MOPEB0321
<table>
<thead>
<tr>
<th>Drug with potential optimization</th>
<th>Clinical trial name (phase, sponsor)</th>
<th>Completed or planned completion</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz 600 vs 400 QD</td>
<td>ENCORE-1, phase 3 (Kirby Institute, Australia)</td>
<td>Lancet (2015) Puls R et al</td>
<td>Non-inferiority (primary endpoint, week 48)</td>
</tr>
<tr>
<td>Zidovudine 600 vs 400 BID</td>
<td>MINIZID, phase 2 (Geneva Univ Hosp, Switzerland)</td>
<td>HIV Med (2015) Rougemont M et al</td>
<td>Less grade 3 and 4 AE in patients with baseline anemia</td>
</tr>
<tr>
<td>Darunavir/r 800 vs 400 mg QD</td>
<td>ANRS-165 DARULIGHT, phase 2 (ANRS, France)</td>
<td>IAS 2017 pilot trial, abstract # MOPEB0313 (Molina JM et al)</td>
<td>Virological efficacy is maintained</td>
</tr>
<tr>
<td>Darunavir/r 400 mg QD</td>
<td>WRHI052 phase 3 (Wits RHI, South Africa)</td>
<td>Enrollment completed (Venter F, personal communication)</td>
<td>? Results expected Q3 2018</td>
</tr>
</tbody>
</table>
Drug optimization: need for age-appropriate formulations

We have a better formulation of LPVr (Indian generic manufacturer)

Efforts are in place to develop FDC to deliver 1st line regimen to children (LPVr/ABC/3TC and EFV/ABC/3TC) (PHTI paediatric HIV treatment initiative partners, Drug for Neglected Diseases)

11 priority products have been identified by WHO and experts from the PADO* group

DTG scored 50 mg tablets could be used for children 14 kg and above - DTG 5 mg dispersible tablets are being tested

### Drug optimization: InSTI Dual therapy

Tested for both naïve and virologically-suppressed patients.

<table>
<thead>
<tr>
<th>Year</th>
<th>regimen</th>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>DTG + 3TC (Paddle, naïve)</td>
<td>1</td>
<td>ACTG 5353 (naïve) # MOAB0107LB PADDLE (naïve) week 96 results # MOPEB0287 DOLULAM week 96 results # MOPEB0322</td>
</tr>
<tr>
<td>2016</td>
<td>CABT LA + RPV LA (LATTE-2)</td>
<td>3</td>
<td>ANRS-163 ETRAL RAL+ ETV # MOPEB0314 48 weeks results</td>
</tr>
<tr>
<td>2017</td>
<td>DTG + RPV (SWORD)</td>
<td>2</td>
<td>CABT LA + RPV LA (LATTE-2) # MOAX0205LB 96-week results</td>
</tr>
<tr>
<td>2017</td>
<td>DTG + RPV (SWORD)</td>
<td>5</td>
<td>DTG + RPV (SWORD) # TUPDB0205 LB Bone mineral density and turnover markers over 48 weeks</td>
</tr>
</tbody>
</table>

Ongoing trials:
- DTG + 3TC<sup>4,5</sup>
- DTG+ FTC<sup>6</sup>
- CABT LA + RPV LA

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2. Llibre JM et al. CROI 2017, 44LB (week 48)
3. Margolis et al., CROI 2017, 31LB (week 32)
4. NCT02831764
5. TANGO trial (ViiV)
6. NCT03160105
7. NCT02938520
8. NCT02951052

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DO WE NEED NEW DRUGS AND FORMULATIONS?
Guidelines help to choose among the few best combinations, and combinations are more efficient in preventing viral rebound. As a result, many of the large manufacturers - Roche, Boehringer Ingelheim and recently Bristol-Myers Squibb - withdrew from HIV research and development.

Few conventional HIV drugs are now concentrated in only a handful of large manufacturers.

*O'Connor J et al, the Lancet HIV, May 2017*
**HIV pipeline in clinical evaluation (viral suppression)**

**Phase I**

- **MK-8591 (EFdA)**
  - Oral nanoformulations
  - NNRTI
  - **Merck**

- **MK-8507**
  - Unknown MOA
  - **Merck**

- **MK-2048**
  - INI
  - **NIH; Merck**

- **PC-1005**
  - (MIV-150/zinc acetate)
  - NNRTI
  - **Population Council**

**Phase II**

- **ABX464**
  - Rev inhibitor
  - **Abivax**

- **GSK2838232**
  - Requires a booster
  - Maturation inhibitor
  - **ViiV**

- **Elsulfavirine (VM1500)**
  - NNRTI
  - **Roche → Virom**

- **Rilpivirine-LAI (TMC278; RPV)**
  - NNRTI
  - PrEP with oral induction
  - **PATH, NIH; Janssen**

- **PRO-140 (PA14)**
  - Not for X4-tropic HIV
  - Entry inhibitor
  - **mAb**
  - **CytoDyn**

- **Sifuvirtide**
  - (FS-0101)
  - Entry inhibitor
  - **Fusogen**

- **Cenicriviroc**
  - (TBR-652; CVC)
  - Not for X4-tropic HIV
  - Entry inhibitor
  - **Takeda → Tobira**

- **Albuvirtide**
  - (FB006M)
  - Entry inhibitor
  - **Frontier Biotech**
  - Filed with **CFDA**

- **Ibalizumab**
  - (TMB-355)
  - Entry inhibitor; mAb
  - **not an ARV**
  - **TaiMed Biologics, Theratechnologies**

- **Dapivirine**
  - (TMC120; DPV)
  - NNRTI
  - **Janssen → IPM**

**Phase III**

- **Fostemsavir**
  - (MK-1439; DOR)
  - NNRTI
  - **Merck**

- **Doravirine**
  - (MK-8507)
  - INI
  - **Merck**

- **Bictegravir**
  - (GS-9883)
  - INI
  - **Gilead, Filed with FDA**

- **Dapivirine**
  - (TMC120; DPV)
  - NNRTI
  - **Janssen → IPM**

- **Cabotegravir-LAI**
  - (GSK-744; CAB)
  - INI
  - PrEP with oral induction
  - **NIH; ViiV**

- **Cabotegravir-LAI + Rilpivirine-LAI**
  - Maintenance strategy with oral induction
  - **ViiV + Janssen**

**Topical microbicide**

- **Oral**
- **Other parenteral**
- **Long-acting injection (LAI)**
- **Topical microbicide**

**Potential first-in-class**

- **VRC-01**
  - bNAb
  - **Rockefeller Univ.**

**Planning stage?**

- **VRC-01**
  - bNAb
  - **Rockefeller Univ.**

**Medicines Patent Pool.**

- **Last updated on:** 5/30/2017

**List not exhaustive.**

- Shock-n-kill, gene/cell therapies, non-oral immunotherapies are not included.

**Rockefeller Univ.**

- **VRC-01**
  - bNAb
  - **Rockefeller Univ.**

**Planning stage?**

- **VRC-01**
  - bNAb
  - **Rockefeller Univ.**
PHASE 1 – a new nucleoside NRTTI* MK-8591 (EFdA)

Nucleoside reverse transcriptase translocation inhibitor – inhibits retrotranscriptase by preventing translocation

**MK-8591 (phase 1b):**
A single once-weekly 10 mg oral dose results in 1.6 log decrease in VL at days 7-10

Perspectives

- Low dose is amenable to extended-duration parenteral formulation
- >180-day extended release from solid formulations (implant) after a single injection in rats (Grobler et al, CROI 2016)

Greater rate and extent of initial viral load decline with a single MK-8591 dose than with QD TAF or TDF

*EFdA* Nucleoside reverse transcriptase translocation inhibitor – inhibits retrotranscriptase by preventing translocation

(Grobler et al, CROI 2016)
HASE 3 - Fostemsavir (GSK3684934) - Attachment inhibitor

Efficacy At Week 96: Observed Analysis

Proportion of subjects with HIV-1 RNA <50 c/mL at week 96

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Proportion</th>
<th>Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK3684934 1200 mg QD</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>ATV/r 300 mg/ 100 mg QD</td>
<td>90%</td>
<td></td>
</tr>
</tbody>
</table>

(GSK3684934, previously BMS-663068), the prodrug of temsavir (GSK2616713, previously BMS-626529). Langley DR et al. Proteins 2015; 83:331–350. Thomson M et al, Antivir Ther 2016 Dec 6, phase 2b 48 week results
What is the added value of highly potent broadly neutralizing antibodies?

So why is it still worth exploring this field further?

1. Future therapies with multiple bNAbs of higher potency
2. Breakthrough with Ab-resistant strains will remain sensitive to conventional ARVs
3. Potential as immunotherapy similar to the rational of cancer immunotherapy

Median time to rebound > 1000 cp/mL
5 days in VRC01 vs. 26 days in placebo (p = 0.01)

A changing paradigm for the use of new anti-HIV drugs

Formulations with smaller pills, less frequent dosing, long-acting compounds and stronger resistance profiles are underway – with the potential of being cheaper and more accessible. Compounds from new classes – monoclonal antibodies (mAbs), entry inhibitors, maturation inhibitors and capsid inhibitors – are all expected to work for people with multiple drug resistant HIV. Biologicals remain a challenge – and combinations are made possible by a rich pipeline.
Access issues in the context of “TREAT all”
Access to Drugs means Access to Care
(European adults, adolescents from South Africa)

Cascade of care in European Union Countries (-2014)

Access key population – the age issue
The adolescent HIV continuum of care in SA

## Access to ART for children: it takes forever!

<table>
<thead>
<tr>
<th>Drug</th>
<th>Date for Adult Approval</th>
<th>And Children Approval</th>
<th>Delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir DF</td>
<td>2001</td>
<td>2010</td>
<td>9 years</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>2003</td>
<td>2014</td>
<td>11 years</td>
</tr>
<tr>
<td>Darunavir</td>
<td>2006</td>
<td>2011</td>
<td>5 years</td>
</tr>
<tr>
<td>TAF (FDC)</td>
<td>2016</td>
<td>NA</td>
<td>?</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>2007</td>
<td>2013</td>
<td>6 years</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>2011</td>
<td>NA</td>
<td>?</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>2012</td>
<td>NA</td>
<td>?</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>2013</td>
<td>2017 (partial)</td>
<td>5 years</td>
</tr>
<tr>
<td>TAF (FDC)</td>
<td>2016</td>
<td>NA</td>
<td>?</td>
</tr>
</tbody>
</table>

In not a single instance, have there been important differences in efficacy or safety between adults and children. Is it not time to change the paradigm, and assume that new drugs approved for adults can be used in children, until proven otherwise?

Burger and van Rossum. Adapted from Improved labelling of antiretrovirals for paediatric use. Lancet HIV. October 2016.
**Drug costs: Ending the HIV exceptionalism**

**The three 90s revisited “$90 $90 $90”**

**Getting fair prices to treat HIV, hepatitis B and C:**

- **< $90** per year to treat HIV with newer drugs (DTG-combination with XTC/TAF)
- **< $90** per year to treat hepatitis B (TDF/3TC or entecavir)
- **< $90** for 12-week course of HCV (Sofosbuvir/Daclatasvir)

[Map showing percentage of projected ARV costs that are estimated to be unfunded]

- **0%**
- **18%**
- **36%**
- **55%**
- **73%**
- **91%**

**Nearly US$ 4.2 billion of ARV requirements across 38 countries remain unfunded from 2016 to 2020**

*Courtesy, Andrew Hill*

*Arin Dutta and Catherine Barkers, courtesy*
Geographical access:
Patent and Licensing Status of dolutegravir and TDF/3TC/DTG

Countries in DTG adult license

Other countries without patents on DTG

SOURCES: MedsPal; B. Baker, Beyond The Obvious – Direct And Indirect Territorial Coverage Of MPP/Viiv Voluntary License For Dolutegravir
WHAT ARVxs CANNOT DO!
ART will not cure HIV, novel strategies needed:

1. Limit reservoir formation
2. Reduce size of reservoir
   - Render cells HIV-resistant
   - Enhance immune response
   - Flush out reservoir (and remove infected cells)

Next level of multimodality HIV treatment:
- Broadly neutralizing antibodies
- Vaccines
- Immune checkpoint inhibitors
- Latency reversing agents
- Gene therapy
- Hematopoietic stem cell transplantation

Sustained viral remission

HIV eradication (?)
Differences in life expectancy across educational levels emerged with the introduction of ART.

HIV-positive people with higher education had an estimated life expectancy similar to individuals from the general population with only compulsory education.

Gueler A et al, AIDS 2017
The overall prevalence of tobacco use is highest in both men and women living with HIV than in HIV-negative individuals — 50% in Swaziland.

Men who start ART at age 40 AND quit smoking gain 5.7 more years compared with men who continue tobacco consumption.

In patients aged 65 or more, Excess mortality and loss of life years is higher in relation with smoking than HIV related factors.

"From the outset, the epidemic was diverse, and involved populations that were vulnerable, that were marginalized, and somehow the virus had this unique and diabolic way of finding them"
Factors hampering the worldwide response to the AIDS pandemic

- Entry or residence restriction in certain countries for HIV-positive persons
- Gender inequity
- Criminalization of some aspects of sex work
- Detention centres for intravenous drug users
- Same-sex relationship criminalization

Factors hampering the worldwide response to the AIDS pandemic
An AIDS-free generation

- We have never been so close from a Universal Regimen
- We have arguments to challenge the continuous and lifelong use of oral conventional 3-therapy
- Newer drugs with new mechanisms of action and (child-adapted) formulations will meet the need for improved regimens
  - A menu of options may be beneficial to a patient-centered approach (as for contraception)
- Academic-led research should be supported, to provide long-term data, to improve access to care and quality of life, and to reduce social inequities.
- Beyond antiretrovirals, there are still many outstanding challenges to achieve a generation without (fear of) AIDS
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- Rosemary Sudan
- Leticia Moraes

- In memoriam
  Marc Wainberg
Merci pour votre attention!
Are we ready for the universal adoption of the WHO alternative options?

**YES,** with some remaining uncertainties

<table>
<thead>
<tr>
<th>Alternative options in the WHO 2015 Guidelines</th>
<th>The challenges</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz (EFV) 400 mg</td>
<td>(1) Pregnancy?  &lt;br&gt; (2) HIV-TB co-infection</td>
<td>IAS 2017, abstract # 5612 (« within range of those measured for EFV 600 mg during 3rd trimester »)  &lt;br&gt; Ongoing (NCT02832778)</td>
</tr>
<tr>
<td>Dolutegravir (DTG) 50 mg</td>
<td>(1) Pharmacokinetic and outcome during pregnancy  &lt;br&gt; (2) HIV-TB co-infection  &lt;br&gt; (3) First line studies in LMIC?  &lt;br&gt; (4) Long term safety issues</td>
<td>Ongoing (NCT02245022)  &lt;br&gt; IAS 2017, abstract #5532  &lt;br&gt; Ongoing (NCT02178592)  &lt;br&gt; Ongoing (NAMSAL- ANRS; ADVANCE)</td>
</tr>
</tbody>
</table>

Vitoria et al, JIAS 2016, Cohn J et al, AIDS 2015

*Lamorde M et al, abstract # 5612, Molloy S et al, #5532 (Botswana)*
Geographical access: countries that will be able to procure TAF/XTC/DTG from generic sources in the framework of MPP licenses.