NEW ANTI [RETRO] VIRAL DRUGS ... AND STRATEGIES

Alexandra Calmy, MD, PhD
Geneva University Hospitals, Switzerland
Glasgow plenary session,
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Unrestricted education 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

Not a patent holder

PI of the SIMPL’HIV study (NCT03160105)

Consultant for the WHO HIV guidelines (2015-2018)

Member of the French ANRS committee for protocol selection (CSS13)

Member of the Swiss Federal Commission for Sexual Health (EKSG)
Ending AIDS
Promises and limitations of the 90-90-90 approach
International Community
2020 Objectives

Peter Piot’s phone number?

90-81-73
Promises and limitations of the 90-90-90 approaches

73% is the target viral suppression benchmark for 2020 under the 90-90-90 approach

“

It is increasingly clear that the 90-90-90 approach on its own will be inadequate to end the epidemic. **Not only the target of viral suppression are not reached in many part of the world, including high income countries, but the prevention benefit of expanded ART need to be enhanced by other strategic prevention interventions.**

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A Commission by the Lancet, July 2018, IAS
Where are we now?

- Week-48 efficacy improved from 57.2% in studies commencing in 1994-2000 to 83.8% in those commencing after 2010.

- Efficacy at 96 and 144 weeks was 63.5% at Week 96 and 61.8% at week 144, with post-2010 efficacy at weeks 96 and 144 of 79.9% and 77.1%, respectively.

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Andrew Carr et al, AIDS 2018 (in press)
Tens of millions of people will require sustained access to antiretroviral therapy for decades to come.

- 10%: How to reach the 10% not knowing their HIV status
- 10%: How to incentivize those who know their status to reach health care
- 10%: How to ensure a durable suppression regardless of previous ART exposure?

Reaching the 10-10-10 will determine the future of the epidemic.
What could be the answers of the 2018 HIV research landscape?
2018 has been an important year for HIV research with 5 drugs or combo, including the first in class monoclonal Ab (ibalizumab) – One drug has been approved only for use in China (albuvirtide, injectable fusion inhibitor)
The 2018 (active) pipeline

Phase I
- **GSK3640254**
  - Maturation Inhibitor
  - GSK
- **MK-4250**
  - MOA unknown
  - Merck
- **MK-8504**
  - NRTI (TFV prodrug)
  - Merck
- **MK-8527**
  - MOA unknown
  - Merck
- **MK-8583**
  - NRTI
  - Merck
- **Vesatolimod (GS-9620)**
  - TLR7 agonist / Immunomodulator (not an ARV)
  - Gilead
- **Vicriviroc (MK-4176) ± MK-2048**
  - Entry Inhibitor ± INI
  - NIH; Merck
- **PC-1005**
  - (MIV-150+zinc acetate)
  - Multipurpose gel including for PreP NNRTI
  - Population Council; NIH

Phase II
- **ABX464**
  - Rev inhibitor
  - Abivax
- **GSK2838232**
  - Requires a booster
  - Maturation Inhibitor
  - GSK
- **MK-8591 (EFdA)**
  - NRTI
  - Merck
- **GS-9131**
  - NRTI
  - Merck
- **Cenicriviroc**
  - (TBR-652; CVC)
  - Not for X4-tropic HIV Entry inhibitor
  - Gilead
  - Tozeda → Tobira
- **VRC01**
  - bNAb against gp120
  - NIH

Phase III
- **Dapivirine (TMC120; DPV)**
  - IVR for PreP NNRTI
  - Janssen → IPM Filed with EMA
- **PRO-140 (PA14)**
  - Not for X4-tropic HIV Entry inhibitor; mAb (not an ARV)
  - CytoDyn
- **UB-421**
  - (TMB-355)
  - mAb against CD4 (not an ARV)
  - United Biopharma

**Potential first-in-class to reach market**
- Topical microbicide
- Oral
- Other parenteral
- Long-acting (LA) parenteral
- Being studied in adolescents and/or children

Medicines Patent Pool
List not exhaustive. Last updated on: 9/2018
A phase Ib trial

*Two bnAbs better than one*

- Phase Ib clinical trial (n=9)
  - Three injections at 0, 3 and 6 weeks of two potent broadly neutralizing antibodies that target independant sites on the HIV-1 envelope spike

The combination of the antiHIV-1 monoclonal Abs 3BCN117 and 10-1074 maintains viral suppression several weeks in the absence of ART

A phase III molecules with new mechanisms of action

**Fostemsavir**

- Fostemsavir (prodrug of temsavir) is a first-in-class attachment inhibitor that binds to HIV-1 gp120, **preventing initial viral attachment and entry** into the host CD4+ T-cell.

**Baseline exposure to ARVs**

**Results disaggregated according to disease characteristics**

**Baseline Viral Load, c/mL**

- **Randomised Cohort (N=272)**
- **Non-randomised Cohort (N=99)**

**Baseline CD4+ T-cell count, cells/µL**

Cabotegravir-LA/rilpivirine-LA in a maintenance strategy have consistently presented encouraging long term data (week 160) (Margolis et al, J Int AIDS Soc 2018, 21(S8):e25187, P118)

- Good CNS penetration (Letendre et al, J Int AIDS Soc 2018, 21(S8):e25187, 0346) but some concerns:
  - the dosing volumes (3mls intra muscularly in the current formulation)
  - the need for oral lead
  - and the deliverability of injections that is resource-intensive (staff time, frequent visit clinics with dosing frequency every 1-2 months etc.)
Cabotegravir, rilpivirine: the pioneer for new administration routes

We have the potential to revolutionize how to deliver ART

Injections
Ex. current formulation of cabotegravir and RIL

Implants
Ex. MK 8591, TAF

Children adapted granules

Vaginal/rectal gel

Vaginal ring

Courtesy: adapted from Jean-Michel Molina, Genève, HIV and the Body, 7 décembre 2017
We have the potential to revolutionize how to deliver ART
Towards an informed choice of different routes of administration

"The contraceptive failure rate among participants using pills, patch, or ring was 4.55 per 100 participant-years, compared with 0.27 among participants using long-acting reversible contraception."

In summary: possible positioning new drugs and combinations in the HIV treatment sequence and needs

<table>
<thead>
<tr>
<th>Indication</th>
<th>Drugs</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve patients</td>
<td>D/C/F/TAF, BIC/F/TAF, DTG/3TC, DOR/TDF/3TC, GS-9131?</td>
<td>Many good alternatives in early lines – universal?</td>
</tr>
<tr>
<td>Patients previously exposed to ARVs</td>
<td>Recycling NRTIs? D/C/F/TAF, DOR/TDF/3TC, BIC/F/TAF?</td>
<td>MK-8591</td>
</tr>
<tr>
<td>Maintenance strategy</td>
<td>Cabotegravir/RIL LA, DTG/3TC</td>
<td>Dual therapies – improved adherence in specific populations? (adolescents)</td>
</tr>
<tr>
<td>Patients with MDR viruses</td>
<td>Ibalizumab, Fostemsavir, MK-8591, GS-9131, mABs</td>
<td>New mechanisms, all mABs</td>
</tr>
</tbody>
</table>

NRTIs are retaining high levels of efficacy despite the prediction of failure from genotypic resistances*

The **global need** for better HIV treatment means that data to inform their use **in all settings** are needed.
Sequencing options for preferred first-, second- and third-line ART regimens in adults and adolescents (including pregnant women and women childbearing potential)

<table>
<thead>
<tr>
<th>Population</th>
<th>1st line regimens</th>
<th>2nd line regimens</th>
<th>3rd line regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and adolescents (including pregnant and childbearing age women)(^a)</td>
<td>NAMSAL, ADVANCE</td>
<td>D2EFT</td>
<td>DRV/r (^e) + DTG (^g) ± 1-2 NRTIs (where possible consider optimization using genotyping)</td>
</tr>
<tr>
<td></td>
<td>NAMSAL</td>
<td></td>
<td>2 NRTIs + DTG (^b)</td>
</tr>
</tbody>
</table>

\(^a\) Optimized NRTI backbone should be used: AZT following TDF or ABC failure, and vice-versa.
\(^b\) In childbearing age women an adolescent girls, DTG can be used in those on reliable contraception and fully informed and benefit outweighs the risk.

- By July 2018, **71 LMICs (51%)** informed that have included or are planning to include DTG in their national guidelines
- Approximately 500 000 PLHIV are using DTG globally

*Courtesy WHO guidelines, Meg Doherty, IAS 2018*
ViiV sponsored and independent trials of dolutegravir

Trials where participants are:

- 50% white
- >70% male (except ARIA)
- >75% VL <100,000
- 100% CD4 >300

ViiV DTG Randomised clinical trials
n=6912

naïve
- SINGLE, n=833
- SPRING-2, n=822
- ARIA, n=495
- FLAMINGO, n=484
- GEMINI, n=1433

naïve, preg
- GEMINI, n=1433

paediatrics
- ODYSSEY, n=700

Other DTG Randomised clinical trials
n=4700

naïve
- ADVANCE, n=1053
- NAMSAL, n=606
- ADVANZ-4, n=130
- DOLPHIN1/2, n=280
- VESTED, n=639

naïve, preg
- SINGLE, n=833

 naivement

naïve

Courtesy, Andrew Hill
DTG-based clinical trials informing the FDA application

Comparison of baseline characteristics leading to study exclusion

Inclusion/exclusion criteria – GEMINI*:  
- HIVRNA baseline >1000 and < 500’000 cps  
- No CDC stage 3 HIV disease except Kaposi if CD4 are above 200 cells  
- No hepatic impairment/unstable disease  
- No HBV infection or need for HCV therapy  
- Not pregnant, planning to become pregnant, or breastfeeding  
- Use of protocol-approved contraception
  
  « No herbal supplementation leading to potential interactions »
  « active drugs according to genotype »

NAMSAL baseline characteristics  
- 26% of patients included in NAMSAL are staged WHO 3 or 4  
- 10% are AgHbS carriers  
- 31% have a baseline VL above 500’000  
- 7% have CD4 cell count below 50

Baseline HIV RNA matters – the example of TDF/3TC/EFV: efficacy by baseline HIV RNA (<50 copies, week 48)

Gaps on the use of dolutegravir

- IRIS in PLHIV with advanced HIV disease
- Unwanted weight gain

HIV-associated TB: need to double dose if rifampin is used

Pregnant/BF women: 1 million of pregnant women in need of ART worldwide in 2017

Infants and children: safety and dose finding trial underway.

Resistance to DTG: a chink in the armor?

- In cohort studies not detected in RCTs (other INSTIs)* - weight gain observed in RCTs
- No data on TAF LD One Industry-sponsored non comparative study
- 5-years lag between acceptance of a drug and data in pregnancy
- 10-years lag between acceptance of a drug and data different age groups
- The apparently high genetic barrier to resistance of dolutegravir may be breached when the drug is given as monotherapy (Dan Kuritskes)

Adapted from Doherty M, WHO symposium, IAS 2018
Two safety alerts related to the use of ARVs during pregnancy in 2018
NEW STUDY
suggests risk of birth defects in babies born to women on HIV medicine DTG (EMA, 18.05.2018)

The European Medicines Agency (EMA) has recently confirmed (October 5th) its earlier precautionary advice

- **Do not prescribe** dolutegravir to women who have the potential to bear children
- Advise women who have the potential to bear children to use effective contraception throughout DTG treatment.


NEW CONTRAINDICATION
against using darunavir/cobicistat during pregnancy

- This new contraindication is based on significantly reduced plasma levels of darunavir and cobicistat during the second and third trimesters of pregnancy.
  - Darunavir can still be used during pregnancy, but only when boosted by ritonavir

Countries guidance revision on DTG 1st line: WLHIV initiating DTF based regimen as of 4th Sept 2018

*Several countries defined WCBA as women 10-49 years old or in pre-menopausal period
** 6 countries recommend Pregnancy test to be performed before starting WCBA on DTG based regimen
You are taking ART that includes EFV. You have side effects that you can live with but prefer to avoid.

Your healthcare worker explains that they want to keep your ART as a fixed dose combination that contains EFV. The reason for this is that in the country where you live, the MoH has made a temporary decision that women and girls with childbearing potential should avoid DTG to the potential risk of birth defects.

Other people are being switched to ART that contains DTG because it is considered to be an effective drug, has fewer side effects, is cheaper for the country to provide, and over time HIV is less likely to become resistant to it.

How would you feel?
What did we learn?

Women are not a special population:

☑ The challenge of a women-centered approach to reproductive health
☑ Most countries chose EFV for PW (gender specific recommendations)

Guidelines:

☑ Guidelines had to adapt to the release of new data
☑ Guidelines have a different role and target when compared to medicine agency safety alerts.
  ✔ Guidelines are patient centered
  ✔ Safety alert are drug centered

« 16% had an unintended pregnancy while on contraception (...). Of these, 68.1% terminated the pregnancy and almost half continued using the same contraceptive method after the event »
Tensions in the search for a universal treatment
Obstacles for delivering a single « one-size-fits-all » antiretroviral treatment

- Gender-based recommendations
- Guidelines interpretation varies across countries
- Community leaders rightly point out that it is « time to realise (our) sexual and reproductive health and rights »
- Guidelines recommend « give people choices and options »
- HIV research is active and new strategies are emerging
The case of dual therapy trials in the era of differentiated care, who still need 3DR to reach/or maintain a SUPPRESSED VL?
Successful (% difference less 12% between arms), treatment experienced, maintenance dual therapies randomized trials including more than 100 patients (in green – unpublished)

5. Llibre et al, The Lancet, March 3rd, 2018
Who are we excluding from treatment simplification trials?

At present, it remains necessary to select those individuals with the best chances to maintain an suppressed viral load under a "reduced" treatment

1. AgHbS+ carriers are not eligible to dual therapies including only one NRTI (MK-8591?)
2. Pregnant women
3. Advanced HIV diseases
4. Previous virological failure

Open questions

1. Patients who do not benefit from frequent viral load monitoring in RLS may not be suitable for reduced or short-cycle therapies
2. What about patients with an unknown HIV history? Role of archived mutations?
Is a personalized approach feasible at large scale to achieve a universal health coverage?

There is no doubt that a robust, people-centered health system is needed to end communicable diseases.
Changing the face of clinical trials?
The case of switch studies

Maintaining virological suppression is not the only endpoint to assess treatment efficiency

Maintaining virological suppression is not a benefit – using only this one criterion should not be encouraged

– Virological efficiency is best judged in clinical trials of treatment-naive patients than in trials of therapeutic strategies and it is reassuring to note several dual-therapy trials conducted in treatment-naive patients (or «in this population»?)

– Switch and simplified maintenance studies may benefit from quality of life, toxicity or drug interactions improvements, cost-effectiveness, and number-needed-to-treat-to-benefit analyses.

Venter, Hill Lancet 2018,
Andrew Carr et al, the Ethics of Switch/Simplify in Antiretroviral Trials: Non-Inferior or Just Inferior? PLoS one, July 17, 2012.
The case of Phase 3 trials

Phase III trials are overestimating treatment success – a systematic review of initial ART

- Randomized trials or cohorts of initial ART from 1994 to 2017
- 77'999 patients included for week 48 analyses
- 17'034 included for the week 144 analyses

Generating and challenging evidenced-based data

- 40 clinical trials have been reported in this short review
- 20 reviews or editorial articles have been cited
  - Master the energy necessitated by the conduct of clinical trials
  - Are all data generated useful? Reported? Publically available?
- Multiplying the study secondary endpoints is the way forward?
Trends in clinical trial costs

Mean total cost per study volunteer

Nature Reviews | Drug Discovery
The mean number of distinct procedures carried out per protocol increased significantly for phases I, II and III protocols.

The mean number of planned visits per study volunteer grew at a far more modest rate, resulting in more procedures performed per study volunteer visit and a greater burden on volunteer participation.

Getz KA, Campo RA, Nature reviews drug discovery May 2017
The right balance needs to be found

Between the necessity to assess important variables

...and the collection of excessive and unnecessary clinical data

- that may compromise data integrity and analysis,
- lead to higher error rates,
- drive longer study duration and
- delay submissions to regulatory agencies.

✓ Solliciting feedback from patients and investigator sites
✓ Emphasize home-collected data
✓ through the use of secured connected tools
✓ Coordinated research efforts
✓ Master protocols

*Drazen JM et al, New Engl J Med 2017*
A patient-centric research approach

"if research is to fulfill its goal of being patient centric, it will be necessary to leverage technological advances such as mobile health (...) to capture the patient experience (...) beyond the controlled confines of traditional randomized clinical trials."

Jacqueline Corrigan-Curay et al, JAMA 13 August 2018
HIV exceptionalism – How has HIV research contributed to advances way beyond of the field?
How the antiretroviral agents catalyzed drug discovery for other viral diseases

1. The most obvious and impactful contribution is the study of hepatitis C viruses

2. The approach of developing small molecules that attach to the viral enzyme targets was perfected with HIV medications and directly applied to HCV (direct acting antiviral agents)

3. This also applies to Ebola and other flaviviruses
The clinical response to depression suffers from a “treatment cascade”: the affected individual must access health care, be recognized clinically, initiate treatment, receive adequate treatment, and respond to treatment.
2018 is an important year for HIV research

- Newer drugs with new mechanisms of action and (child-adapted) formulations will meet the need for improved regimens
  
  - Reaching the remaining 10-10-10 will require large efforts from all stakeholders, including clinical researchers
  - Options for heavily pretreated patients are becoming reality
  - A menu of options may be beneficial to an individualized approach (as for contraception)
  - HIV response demonstrated the importance of transforming health system fit for the purpose of delivering people-centered care for diverse population including the most marginalised.
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The use of treatment cascade

**Depression**  
*Pence et al, Curr Psychiatry Rep. 2012*

**Hypertension**  
*Attoei et al, Lancet 2017*

[Diagram showing the treatment cascade for depression and hypertension with percentages and availability data for different regions.]

*Figure 1: Availability of BP-lowering medicines in 526 PURE communities*
The impact of M184V mutation in patients switched onto a DTG/ABC/3TC regimen

There was no significant difference in the VF risk among those with or without M184V in univariate analysis.

Olearo et al, LB Glasgow 2018
Successful (% difference less 12% between arms), treatment experienced, maintenance dual therapies randomized trials including more than 100 patients (*in green – unpublished*)

5. Llibre et al, The Lancet, March 3rd, 2018
8. Pinola M, J of Antivirals and Antiretrovirals, 2019

- **Salt¹, n=286**
- **Ole², n=250**
- **Dual GESIDA³, n=249**
- **ATLAS M⁴, n=250**
- **bPI+ 3TC**
- **bPI+ TDF**
- **Kalead⁸, n=167**
- **Sword 1-2⁵, n=1028**
- **LATTE⁶, n=243**
- **LATTE-2⁷, n=286**
- **ATLAS-2M (NCT03299049)**
- **ATLAS (NCT02951052)**
- **FLAIR (NCT02938520)**
- **INSTI+NNRTI**
- **SIMPL’HIV (NCT03160105)**
- **TANGO (NCT03446573)**
- **TRIDUAL (NCT03447873)**
- **DTG+3TC**
- **DTG+FTC**
- **bPI+INSTI Dualis (NCT02486133)**

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5. Llibre et al, The Lancet, March 3rd, 2018
8. Pinola M, J of Antivirals and Antiretrovirals, 2019
Despite the lack of comparison with tenofovir alafenamide-based 3-drug regimens, the 2-drug regimens showing consistent non-inferiority and safety versus 3-drug regimens will challenge the current paradigm of 3-drug ART.
What did we learn?

- The challenge of gathering good quality data: from pharmacovigilance – use of retrospective data - prospective cohorts – basic science
- The difficulty of standardizing concept: the variability of “consistent” contraception

Guidelines:

✓ Guidelines had to quickly adapt to the release of new data
✓ Guidelines have a different role and target when compared to medicine agency safety alerts. Guidelines are patient centered – Safety alert are drug centered (more restrictive)
✓ Development of community translation of the WHO ARV guidelines update

Pregnant women:

✓ Most countries chose EFV for PW (gender specific recommendations): what about women identified late in pregnancy when DTG could give the higher benefit?
Are you satisfied with your current treatment?

- Based on observed case dataset of subjects who completed Week 32 questionnaires.
- HIV Treatment Satisfaction Questionnaire HIVTSQc

What do people want? Variables influencing antiretroviral treatment selection

Ylverton et al, AIDS PATIENT CARE and STDs Volume 32, Number 9, 2018
Google doctor

Does googling lead to statin intolerance?

- The nocebo effect in observational studies: when patients have expectations of adverse effects, they are more likely to experience them.

- The nocebo effect driven by Google may be contributing to statin intolerance, resulting in patients who might otherwise benefit foregoing a cardiovascular risk reduction of up to 50%

A drug for patients exposed to MDR viruses

*Ibalizumab – a non competitive entry inhibitor binding to CD4*

- Active against HIV-1 resistant to all approved ARV agents
- Initial development as IV infusion to be administered every 2 weeks
- Functional monotherapy and q14 days as maintenance regimen

30 centers US and Taiwan
N=40 (31 completed all scheduled visits
VL>1000 cp, MDR 3 classes (1 drug)

1st endpoint: proportion of patients who had a decrease in VL of at least 0.5 log from baseline to day 14

33 (83%) reached the primary endpoint

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*Emu B et al, J Int AIDS Soc 2018, 21(S8):e25187, 0345*