Have we won the clinical battle against HIV drug resistance?

The Case For

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Disclosures

• Dr Milinkovic has received honoraria for consultancy and speaker services from: Gilead Sciences, Janssen and VIIV Healthcare, as well as support for conference attendance from Gilead Sciences and Janssen
Approved medications for HIV infection: 1996–2019

Protease inhibitors
Integrase inhibitors
Nucleoside reverse transcriptase inhibitors

Non-nucleoside reverse transcriptase inhibitors
Entry inhibitors

Fixed dose combination

Year of European licensing

1996
- stavudine
- lamivudine*
- ritonavir
- indinavir

1997
- nevirapine
- efavirenz
- abacavir

1998
- abacavir/lamivudine*/zidovudine
- lopinavir
- lopinavir/ritonavir

1999
- abacavir/lamivudine*/zidovudine
- lopinavir
- lopinavir/ritonavir

2000
- abacavir/lamivudine*/zidovudine
- lopinavir
- lopinavir/ritonavir

2001
- abacavir/lamivudine*/zidovudine
- lopinavir
- lopinavir/ritonavir

*No longer available for use in the European Union

ARVT for treatment-naïve PLWH have demonstrated long-term, durable efficacy*

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Week 0</th>
<th>Week 48</th>
<th>Week 96</th>
<th>Week 144</th>
<th>Week 192</th>
<th>Week 240</th>
</tr>
</thead>
<tbody>
<tr>
<td>STARTMRK(^1)</td>
<td>281</td>
<td>86%</td>
<td></td>
<td></td>
<td>71%</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>76%</td>
<td></td>
</tr>
<tr>
<td>ARTEMIS(^2)</td>
<td>689</td>
<td>84%</td>
<td>80%</td>
<td></td>
<td>69%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>72%</td>
<td></td>
</tr>
<tr>
<td>104/111(^3)(^-)(^5)</td>
<td>866</td>
<td>92%(^3)</td>
<td>87%(^4)</td>
<td></td>
<td>84%(^5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SINGLE(^6)</td>
<td>414</td>
<td>88%</td>
<td>80%</td>
<td></td>
<td>71%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECHO-THRIVE(^7)(^,)(^8)</td>
<td>686</td>
<td>83%(^7)</td>
<td>78%(^8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


ARV, antiretroviral; COBI, cobicistat; DRV, darunavir; DTG, dolutegravir; EVG, elvitegravir; FTC, emtricitabine; r, ritonavir; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.


Strategies are not intended to be compared directly.
# Zero HIV resistance in recent 3DR trials

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Study duration</th>
<th>Resistance-associated mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment-naïve PLHIV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1489¹</td>
<td>314/315</td>
<td>48 weeks</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>BIC/FTC/TAF DTG/ABC/3TC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1490²</td>
<td>320/325</td>
<td>48 weeks</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>BIC/FTC/TAF DTG + FTC/TAF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMBER³</td>
<td>362/363</td>
<td>48 weeks</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>DRV/COBI/FTC/TAF DRV/COBI/FTC/TDF</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td><strong>Virologically-suppressed PLHIV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1844⁴</td>
<td>282/281</td>
<td>48 weeks</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>BIC/FTC/TAF DTG/ABC/3TC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMERALD⁵</td>
<td>763/378</td>
<td>48 weeks</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>DRV/COBI/FTC/TAF Boosted PI + FTC/TAF</td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

# Resistance: DTG + 3TC

<table>
<thead>
<tr>
<th>Overall N</th>
<th>Study type</th>
<th>Resistance in DTG + 3TC arm, n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment-naïve</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTG A5353(^1)</td>
<td>120</td>
<td>Phase II, single-arm, pilot</td>
</tr>
<tr>
<td>PADDLE(^2)</td>
<td>20</td>
<td>Single-arm pilot</td>
</tr>
<tr>
<td>GEMINI I and II(^3)</td>
<td>1,433</td>
<td>Phase III, randomised, double-blind</td>
</tr>
<tr>
<td><strong>Suppressed switch</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAMIDOL(^4)</td>
<td>104</td>
<td>Open-label, single-arm</td>
</tr>
<tr>
<td>ASPIRE(^5)</td>
<td>89</td>
<td>Open-label, randomised</td>
</tr>
<tr>
<td>DOLAM(^6)</td>
<td>91</td>
<td>Open-label, randomised</td>
</tr>
<tr>
<td><strong>Real world</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borghetti(^7)</td>
<td>484</td>
<td>Single centre cohort</td>
</tr>
<tr>
<td>DOLULAM (^8)</td>
<td>27</td>
<td>Prospective cohort</td>
</tr>
<tr>
<td>Maggiolo(^9)</td>
<td>94</td>
<td>Prospective cohort</td>
</tr>
</tbody>
</table>

Real World Evidence suggests that INSTI class resistance is Low

Evaluation of the prevalence of baseline resistance testing and TDRMs in 36,288 PLWH (2013-2016)

- Prevalence of TDRM regardless of ARV class was stable.
- TDRM for INSTIs was infrequent (1.1%) with the lowest prevalence among all drug classes.

Baseline INSTI resistance testing increased from 3.7% to 23.0% (p<0.001)

**Most Common TDRMs**

<table>
<thead>
<tr>
<th>Classes</th>
<th>&gt; 10%</th>
<th>5-9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSTI</td>
<td>N155H (18%), R263K (18%), E92Q (14%)</td>
<td>Q148H, G140S, S147G, Y143H</td>
</tr>
<tr>
<td>NNRTI</td>
<td>K103N (72%)</td>
<td>Y181C, G190A, K103S, P225H</td>
</tr>
<tr>
<td>NRTI</td>
<td>M41L (22%), T69N (17%), T215S (14%), M184V (11%)</td>
<td>T215C/D/E, D67N, T69A, K219Q, L210W, E44D</td>
</tr>
<tr>
<td>PI</td>
<td>L90M (24%), Q58E (19%), V11I (12%), T74S (11%), M46I/L (10%)</td>
<td>D30N, N88D</td>
</tr>
</tbody>
</table>

*Descending order of prevalence*

† National HIV Surveillance System (U.S.)

What about the impact of archived resistance in virologically suppressed patients that need a therapy switch?
Viral Dynamics May Influence the Risk of Viral Transmission or Selection of Resistant Variants

Viral Decay Rates

Viremia = theoretical risk of transmission and resistance

Weeks

Viral load, $\log_{10}$

3-drug regimen
2-drug regimen

SPRING-1/SINGLE, $\leq 100,000$ c/mL (n=321)
SPRING-1/SINGLE, $> 100,000$ c/mL (n=146)
A5353, $\leq 100,000$ c/mL (n=83)
A5353, $> 100,000$ c/mL (n=37)

Weeks

Viral load, $\log_{10}$
Conclusions

- Current ARVT protects from potential selection of mutants (e.g. M184V), through its high antiretroviral potency and its high barrier to resistance
- Current ARVT fully inhibits ongoing cycles of viral replication by its good antiretroviral potency and favourable PK properties
- Once HIV replication is fully blocked, emergence of resistant mutants is unlikely
- DTG + 3TC is a prime example of *in vivo* synergism mediated by multiple distinct mechanisms
- 2DRs showed comparable barrier to resistance versus triple drug regimens in treatment-naïve patient populations
Unanswered questions ??

Data in special populations?

• Women (510 participants - VAWES and OLE study in women): No emergent resistance mutations detected

• Children and Adolescents (Study 380-1474): No emergent resistance mutations detected

• TPLWH (TIME Study)

• >50 years old (high genetic barrier drugs)

Low-income and middle-income countries (1100 participants ADVANCE Study)

3. Boffito et al. Study in set up
4. Boffito&Milinkovic :Multiple studies proposals
5. Francois Venter . Advance study
Conclusions

✦ New drugs currently in use today have shown excellent results: no development of resistance at failure

Pipeline:

✦ Drugs in Phase 3 Development: Long Acting Cabotegravir + Rilpivirine (ATLAS and FLAIR study)
✦ Drugs in Phase 2 Development: Elsulfavirin (subcutaneous formulation in development), Fostemsavir (novel gp120 inhibitor), NRTTI (MK-8591)
✦ Drugs in Phase 1 Development: capsid inhibitors (GS-6297, -6207), Broadly neutralizing antibodies (VRC01-LS)

✦ High genetic barrier – high concentrations (well tolerated) and no development to resistance