ART update: strategies & drugs

Chair: Dr Dan Clutterbuck

Dr Laura Waters
Mortimer Market Centre. London, UK
ART update: strategies & drugs

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Disclosures

• Speaker/advisory fees
  • ViiV, MSD, Janssen, Gilead, Theratech, Cipla & Mylan
• Investigator on Gilead, ViiV, & Janssen sponsored trials
Why are we talking about *when*?
Same day ART: no clear evidence of benefit outside LMIC settings

"supports same day ART"

Er, but it doesn’t!
Within 8 vs within 21 days

Whitlock G et al. HIV Med 2019
Qualitative study: Rwanda

Participants supported a same day approach, but described logistical and emotional challenges

- Trauma related to, & difficulty accepting, HIV diagnosis
- Feeling intimidated at the prospect of lifelong ART
- High rates of early side effects “likely reflecting physiologic or psychosomatic adjustment to medications”
WHAT
DHHS guidelines: December 2019
Recommended for most people with HIV

<table>
<thead>
<tr>
<th>INSTI + 2 NRTI</th>
<th>Key requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAF/FTC/BIC</td>
<td></td>
</tr>
<tr>
<td>ABC/3TC/DTG</td>
<td>HLA B*5701 negative, known HBV status, no HBV co-infection</td>
</tr>
<tr>
<td>DTG + (TAF or TDF) + (3TC or FTC)</td>
<td></td>
</tr>
<tr>
<td>RAL + (TAF or TDF) + (3TC or FTC)</td>
<td></td>
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<table>
<thead>
<tr>
<th>INSTI + 1 NRTI</th>
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<tbody>
<tr>
<td>DTG + 3TC</td>
<td>VL &lt;500,000, HBV negative, HBV &amp; resistance status known</td>
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# EACS guidelines v10.1: October 2020

## Recommended regimens

<table>
<thead>
<tr>
<th>INSTI + 1 or 2 NRTI</th>
<th>Notes &amp; restrictions</th>
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<td>ABC/3TC/DTG or ABC/3TC + DTG</td>
<td>ABC: HLA, CV risk</td>
</tr>
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<td>DTG: weight gain</td>
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<td>TAF/FTC or TDF/XTC + DTG</td>
<td>DTG, TAF: weight increase</td>
</tr>
<tr>
<td></td>
<td>TDF: prodrug types. Renal and bone toxicity</td>
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<tr>
<td>TAF/FTC/BIC</td>
<td>BIC &amp; TAF: weight gain</td>
</tr>
<tr>
<td>TAF/FTC or TDF/XTC + RAL</td>
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<tr>
<td></td>
<td>TAF &amp; RAL: weight gain</td>
</tr>
<tr>
<td>3TC/DTG or XTC + DTG</td>
<td>HBVsAg negative</td>
</tr>
<tr>
<td></td>
<td>VL &lt;500,000</td>
</tr>
</tbody>
</table>

[https://www.eacsociety.org/media/final2021eacsguidelinesv11.0_oct2021.pdf](https://www.eacsociety.org/media/final2021eacsguidelinesv11.0_oct2021.pdf) accessed 27th November 2021
DHHS guidelines: June 2021  
Recommended for most people with HIV

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## EACS guidelines v11.0: October 2021

### Recommended regimens

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</thead>
</table>
| ABC/3TC/DTG or ABC/3TC + DTG | ABC: HLA, CV risk  
DTG: weight gain |
| TAF/FTC or TDF/XTC + DTG | DTG, TAF: weight increase  
TDF: prodrug types. Renal and bone toxicity |
| TAF/FTC/BIC | BIC & TAF: weight gain |
| TAF/FTC or TDF/XTC + RAL | TDF: prodrug types. Renal and bone toxicity.  
TAF & RAL: weight gain |
| 3TC/DTG or XTC + DTG | HBVsAg negative  
VL <500,000 |

<table>
<thead>
<tr>
<th>NNRTI + 2NRTI</th>
<th>Notes &amp; restrictions</th>
</tr>
</thead>
</table>
| TAF/FTC or TDF/XTC + DOR or TDF/3TC/DOR | TDF: prodrug types. Renal and bone toxicity.  
TAF: weight increase  
DOR: HIV-2 caveat |

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Key elements of DHHS & EACS guidelines

FTC = 3TC
TDF = TAF
Weight gain: implicated drugs

- **INSTI: particularly 2\textsuperscript{nd} generation**
  - 1\textsuperscript{st} line
    - Relative to efavirenz, yes
    - Relative to other core agents
  - Switch = not clear

- **TAF**
  - 1\textsuperscript{st} line: relative to TDF, yes, and less so to ABC
  - Switch: relative to TDF, yes
DRIVE-AHEAD: weight change

![Graph showing weight change over time for different treatment groups.

Week | Median Change (IQR), kg
---|---
0    | 0.3
24   | 0.7
48   | 1.2
96   | 1.0
148  | 1.9
192  | 2.4

Week | Median Change (IQR), kg
---|---
0    | 2.0
24   | 3.0
48   | 2.4
96   | 1.9
148  | 1.0
192  | 0.3

Sample sizes:

<table>
<thead>
<tr>
<th>Week</th>
<th>n1</th>
<th>n2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>364</td>
<td>364</td>
</tr>
<tr>
<td>24</td>
<td>346</td>
<td>327</td>
</tr>
<tr>
<td>48</td>
<td>323</td>
<td>308</td>
</tr>
<tr>
<td>96</td>
<td>299</td>
<td>277</td>
</tr>
<tr>
<td>148</td>
<td>271</td>
<td>247</td>
</tr>
<tr>
<td>192</td>
<td>256</td>
<td>231</td>
</tr>
</tbody>
</table>
#593: WIHS weight modelling study

- 25% predicted to see ≥5% decrease in BMI following ART switch
- 2 regimens accounted for 97% of ≥5% BMI decrease following switch
  - TAF/FTC + EFV (53%) and
  - TAF/FTC/ATV/r (44%)
- Non ART factors critical

O’Halloran J et al, CROI 2022
Doravirine for persons with excess weight gain on INSTI & TAF

ClinicalTrials.gov Identifier: NCT04636437

Recruitment Status: Recruiting
First Posted: November 19, 2020
Last Update Posted: February 24, 2022
See Contacts and Locations

Planned n=222
Continued ART vs
Switch to DOR + TDF/XTC
Switch to DOR + TAF/FTC
Reminder!

• The first-line ART recommendations are FIRST-LINE
• There are plenty of acceptable choices for:
  • Switch and/or
  • Maintenance
My thoughts

What role does abacavir play in 2022?

What is our threshold for single tablet regimens?

Will ART costs start to INCREASE herein?

If no RAMs & HBV- what does a 2\textsuperscript{nd} NRTI add to DTG?
HOW
Anglocentric bit: national procurement
In a nutshell

MDT requirement for all bar least expensive & all ART must be reviewed in line with new algorithms

EVERYTHING IS PRESCRIBABLE!
Every cloud....BNF list price

<table>
<thead>
<tr>
<th>Active ingredients</th>
<th>Size</th>
<th>Unit</th>
<th>NHS indicative price</th>
<th>Drug tariff</th>
<th>Drug tariff price</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cobicistat 150 mg</td>
<td>30</td>
<td>tablet (POM)</td>
<td>£672.97 (Hospital only)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>• Emtricitabine 200 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Darunavir (as Darunavir ethanolate) 800 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Tenofovir alafenamide (as Tenofovir alafenamide fumarate) 10 mg</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Is there a strong indication for Symtuza?
### NADIA: 96 week data at CROI 2022

<table>
<thead>
<tr>
<th>DTG vs DRV</th>
<th>TDF vs ZDV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dolutegravir non-inferior to darunavir/ritonavir</strong></td>
<td><strong>Zidovudine inferior to tenofovir-DF even with K65R</strong></td>
</tr>
<tr>
<td>VF: 8.5% DTG, 11.3% DRV</td>
<td>VS &lt;400: 92% vs 85%</td>
</tr>
<tr>
<td>DRV: no PI RAMs at VF</td>
<td>VF: 6% TDF, 14% ZDV</td>
</tr>
<tr>
<td>DTG: 9 with INSTI RAMs at VF</td>
<td>ZDV: 6 x INSTI RAMs (5 high)</td>
</tr>
<tr>
<td>(3.5% population, 45% VFs)</td>
<td>TDF: 3 x INSTI RAMs (intermediate)</td>
</tr>
</tbody>
</table>
Long-acting vs daily oral
1 in 100 at year 1

1 in 70 at year 1

1 in 60 at year 2

1 in 40 at year 3
Injectable vs oral virological failure rates

CAVEAT: WE CAN NEVER BE AS CONFIDENT IN ESTIMATES OF ADHERENCE TO ORAL THERAPY AS WE CAN TO HCP-DELIVERED INJECTABLE THERAPY
New appendix to BHIVA interim injectables guidance

**FLAIR (1M vs oral)** where people were started on abacavir/dolutegravir/lamivudine and had to be suppressed at week 20:

- Oral arm
  - Of the failures (n=4): one failed lamivudine/zidovudine + efavirenz with M184V + G190S NNRTI; one failed elvitegravir/cobicistat/emtricitabine/tenofovir with M184I; one failed elvitegravir/cobicistat/emtricitabine/tenofovir with M230I NNRTI; and one failed elvitegravir/cobicistat/emtricitabine/tenofovir with no resistance
  - No additional confirmed virological failures at year 2

- 1M arm
  - 1 in 100 at year 1, all (n=3) with NNRTI resistance, one also with INSTI resistance
  - No additional confirmed virological failures at year 2
The right information is critical

Patient resources

These resources are not meant to be accessed by patients directly. Please do not share resource links to patients.
Practicalities 1

V vs G

Z

Pelvis
Injection site

Iliac crest

gluteus medius

ASIS

gluteus minimus

Tensor fascia lata

Greater trochanter
Practicalities 2

RILPIVIRINE
Store at 5-8 degrees C
Remove 15 mins pre-injection
Cannot be refrigerated again

BMI >30 2”
BMI does not distinguish muscle & fat

23G 1.5”
Practicalities 3

• Viral load monitoring must be in line with trials i.e. at every IMI
• We need to fill some crucial gaps
  • Breastfeeding & pregnancy
  • People with detectable viral loads
  • Optimising administration (ultrasound guidance? TDM?)
  • Will drug-drug interactions be more of an issue than we realise? There are enzymes and transporters in muscle and adipose tissue too.....
• We’ve got a lot of time to learn about long-acting before the next one comes along....
Fostemsavir & ibalizumab

NO ENTRY

Good results in small numbers of HTE people

CD4

££££

NHS
Ibalizumab

• Every 2 weeks
• Administered via homecare as part of the package
• England pending
  • Wales will follow?
• Under consideration in Scotland & Northern Ireland
not
or
Lenacapavir 1st line: CALIBRATE

Treatment naïve
N=182

Key eligibility criteria:
- ARV naïve
- HIV-1 RNA ≥200 copies/mL
- CD4+ cell count ≥200 cells/µL

Open label
Randomized

Treatment Group 1*
n=52
LEN SC Q6M*
F/TAF oral QD
TAF oral QD†

Treatment Group 2*
n=53
LEN SC Q6M*
F/TAF oral QD
BIC oral QD†

Treatment Group 3‡
n=52
LEN oral QD
F/TAF oral QD

Treatment Group 4§
n=25
B/F/TAF oral QD

2° Endpoint
1° Endpoint

LEN + TAF   Two 2DR arms   LEN + BIC
Efficacy at W54 (FDA Snapshot) among participants virologically suppressed at W28

In pooled SC LEN group (TG 1+2: initially in combination with F/TAF, then with TAF or BIC), among participants who were virologically suppressed at Week 28, 93% (91/98) maintained virologic suppression at Week 54.

*1 participant discontinued due to not meeting the protocol criteria of having HIV-1 RNA <50 copies/mL prior to Week 28; 1 participant discontinued on Day 2.
• Emergent LEN resistance in 2/157 (1.5%) participants
  • One participant in TG 2 developed Q67H+K70R (LEN fold change=20) in CA at Week 10, preceded by M184M/I in RT (IDWeek 2021)†
    • Pattern of mutation emergence suggests incomplete adherence to F/TAF
  • One participant in TG 3 developed Q67H (LEN fold change=7) in CA at Week 54
    • Nonadherence to F/TAF as assessed by pill count and drug levels
• Both participants later re-suppressed on a regimen of INSTI + 2 NRTI
CAPELLA: LEN Efficacy by Fully Active Agents and Emergent Resistance

All 8 persons with emergent LEN resistance were high risk for resistance (0 active drugs in OBR, n = 4; inadequate adherence to OBR, n = 4)

<table>
<thead>
<tr>
<th>Emergent LEN Resistance, Randomized Cohort (n=36)</th>
<th>Nonrandomized Cohort (n =36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants meeting criteria for resistance testing</td>
<td>11 (31)</td>
</tr>
<tr>
<td>Emergent LEN resistance</td>
<td>4 (11)</td>
</tr>
<tr>
<td>- M661</td>
<td>4</td>
</tr>
<tr>
<td>- Q67H/K/N</td>
<td>1</td>
</tr>
<tr>
<td>- K70H/N/R/S</td>
<td>1</td>
</tr>
<tr>
<td>- N74D/H/S</td>
<td>3</td>
</tr>
<tr>
<td>- A105S/T</td>
<td>3</td>
</tr>
<tr>
<td>- T107A/C/N</td>
<td>1</td>
</tr>
</tbody>
</table>

Safety concerns

Gilead and Merck Announce Temporary Pause in Enrollment for Phase 2 Study Evaluating an Oral Weekly Combination Regimen of Investigational Islatravir and Investigational Lenacapavir

Foster City, Calif. & Kenilworth, N.J.- November 23, 2021 - Gilead Sciences, Inc. and Merck, known as MSD outside the United States and Canada, are temporarily pausing enrollment in the Phase 2 clinical study (NCT05052996), evaluating an investigational once-weekly oral combination treatment regimen of islatravir and lenacapavir in people living with HIV who are virologically suppressed on antiretroviral

Press release 23rd November 2021
LACK OF EXPOSURE TO GENITOURINARY MEDICINE (GUM) IS LEADING TO A RECRUITMENT CRISIS

1,3 Anna Hartley*, 2–4 Daniel Richardson. 1 Barts Health NHS Trust, London, UK; 2 Brighton & Sussex University NHS Trust, Brighton, UK; 3 British Association for Sexual Health and HIV; 4 Brighton & Sussex Medical School, Sussex, UK
Training must change

General principles of HIV care

Complex HIV care
Specialist HIV input

Integrated long term condition management

- Relevant GIM specialties
- Broader ICS including 3rd sector
Thank you for listening: questions?

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peoplefirstcharter.org