State of the ART: 
Where We Are Now; Where We Are Going

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State of the ART

- What are the current US and WHO Guidelines for treatment of HIV?
- Are two antiretrovirals as good as three? Update on 2-drug therapy
- What are the options in someone who has difficulty taking daily drugs? Long-acting agents in development
- What are new medicines for treating someone with multi-drug resistant HIV?
- What’s on the horizon?
Reproductive Cycle of HIV and Sites of Action of Major Classes of Antiretroviral Medications

Reverse Transcriptase Inhibitors (RTI)
- Nucleoside RTI (NRTIs) – tenofovir, abacavir, 3TC, FTC
- Nonnucleoside RTI (NNRTIs) – efavirenz, rilpivirine, doravirine

Fusion Inhibitors - ENF
- CCR5 Antagonists -- MVC
- CD4 Post-attachment inhibitor -- ibalizumab

Integrase strand transfer inhibitors (INSTI) – dolutegravir, raltegravir, elvitegravir/cobicistat, bictegravir

Protease inhibitors (PI) – darunavir/ritonavir or cobi; atazanavir/ritonavir or cobi

Antiretroviral Therapy 2018: >25 Options in the US

**Nucleoside/nucleotide RTIs**
- Zidovudine, AZT (*Retrovir*)
- Abacavir, ABC (*Ziagen*)
- Lamivudine, 3TC (*Epivir*)
- Didanosine, ddi (*Videx*)
- Stavudine, d4T (*Zerit*)
- Tenofovir, TDF (*Viread*)
- Emtricitabine, FTC (*Emtriva*)
- AZT/3TC (*Combivir*)
- AZT/3TC/ABC (*Trizivir*)
- ABC/3TC (*Epzicom*)
- TDF/FTC (*Truvada*)
- TAF/FTC (*Descovy*)
- TDF/3TC (*Cimduo*)

**CCR5 receptor blocker**
- Maraviroc (*Selzentry*)

**Integrase inhibitors**
- Raltegravir, RAL (*Isentress*)
- Elvitegravir, EVG
- Dolutegravir, DTG (*Tivicay*)
- Bictegravir, BIC

**NNRTIs:**
- Delavirdine (DLV)
- Nevirapine, NVP (*Viramune*)
- Efavirenz, EFV (*Sustiva*)
- Etravirine (*Intelence*)
- Rilpivirine (*Edurant*)

**Fusion inhibitors:**
- Enfuvirtide, ENF or T20 (*Fuzeon*)

**CD4 Post-attachment inhibitor**
- Ibafilizumab (*Trogarzo*)

**Protease inhibitors:**
- Indinavir, IDV (*Crixivan*)
- Saquinavir, SQV (*Invirase*)
- Nelfinavir, NFV (*Viracept*)
- Amprenavir, APV (*Agenerase*)
- Atazanavir, ATV (*Reyataz*)
- Fosamprenavir, FPV (*Lexiva*)
- Lopinavir/ritonavir (*Kaletra*)
- Tipranavir (*Aptivus*)
- Darunavir (*Prezista*)
- Darunavir/cobicistat (*Prexcobix*)
- Atazanavir/ritonavir (*Evotaz*)

**Red – combination agents**

**Single pill combinations (n=9)**
- EFV/FTC/TDF (*Atripla*)
- EFV/3TC/TDF (*Symfi*)
- RPV/FTC/TDF (*Complera*)
- ETV/cobi/FTC/TDF (*Stribild*)
- DTG/ABC/3TC (*Triumeq*)

- **Protease inhibitors:**
- ETV/cobi/FTC/TAF (*Genvoya*)
- Rilpivirine/FTC/TAF (*Odefsey*)
- BIC/FTC/TAF (*Biktarvy*)
- EFV400/3TC/TDF (*Symfi-lo*)

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**Notes:**
- Red – combination agents
- *Evolution of antiretroviral therapy continues: >25 options in the US.*
Choosing An Initial Regimen

- EFV
- RPV
- EVG/cobi
- EFV
- EVG/cobi
- ATV/r
- DRV/r
- ATV/r
- DTG
- BIC
- DTG
- RAL
- DTG
- DRV/r
- RAL
- ATV/r
### What to Start: US Dept of Health and Human Services (DHHS)  
**Updated 2018**

<table>
<thead>
<tr>
<th>Recommended Regimens</th>
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<tbody>
<tr>
<td><strong>Integrase inhibitor + 2 Nucleoside RTI</strong></td>
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Tenofovir: tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF)

[http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf](http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf)
## Recommended Regimens

| Integrase inhibitor + 2 Nucleoside RTI | • Bictegravir/TAF/FTC  
|                                         | • Dolutegravir/abacavir/3TC  
|                                         | • Dolutegravir plus TAF/FTC |

- Fewer long-term safety and efficacy data with BIC than with DTG
- If substantial cost difference, TDF effective and generally well-tolerated, esp. if pt not at high risk for bone, renal disease
  - Differences between TAF & TDF accentuated when TDF is used with booster, RTV or cobicistat

Hill A et al, J Virus Erad, 2018
<table>
<thead>
<tr>
<th>Regimen</th>
<th>PROS</th>
<th>CONS</th>
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<tbody>
<tr>
<td>ABC/3TC/DTG</td>
<td>• Not nephrotoxic</td>
<td>• Must confirm HLA-B5701 neg</td>
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<tr>
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<td>• Single pill combination</td>
<td>• Relatively large pill</td>
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<td>• Some studies, but not all, show association between ABC and cardiac</td>
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<td>events</td>
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<tr>
<td></td>
<td></td>
<td>• NTD concern with DTG</td>
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<tr>
<td>TAF or TDF/FTC + DTG</td>
<td>• TAF has more favorable effects on renal and bone markers than TDF</td>
<td>• Two pills per day</td>
</tr>
<tr>
<td></td>
<td>• Good option for HIV/HBV</td>
<td>• Do not use TAF if CrCL &lt;30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• NTD concern with DTG</td>
</tr>
<tr>
<td>TAF/FTC/Bictegravir</td>
<td>• Single pill combination</td>
<td>• Less long-term data</td>
</tr>
<tr>
<td></td>
<td>• Similar efficacy as ABC/3TC/DTG, DTG + TAF/FTC</td>
<td>• Do not use TAF if CrCl &lt;30</td>
</tr>
<tr>
<td></td>
<td>• Good option for HIV/HBV</td>
<td>• Insufficient data in pregnancy</td>
</tr>
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In the US, what do we use for most people with HIV?
Dolutegravir and Neural Tube Defects (NTD)

- Tsepamo: Birth outcomes study in Botswana
- Interim report (May 1, 2018): 4 infants with NTD born among 426 women who conceived while on DTG
- Update prevalence (July 20, 2018): 4 infants born among 596 women who conceived while on DTG (0.67%)
- Additional data expected by spring 2019

Zash R et al, NEJM, July 24, 2018
Zash R et al, 22nd IAC, 2018, Abst TUSY1502
In US, when might we choose a non-INSTI regimen?

- Patient with uncertain adherence or need to start ART before resistance test available:
  - Boosted PI (DRV/r or DRV/c): high barrier to resistance
- Patient with TB on rifampin-based regimen:
  - Most data with EFV/TDF/FTC
    - Rifampin has less effect on EFV conc. than other ARVs
  - RAL, DTG can also be used (but at increased dose); BIC cannot be used
- When INSTI is not optimal because of side effects or drug interactions
• Doravirine (DOR)
  – NNRTI; active against HIV resistant to 1\textsuperscript{st} gen. NNRTIs
  – Non-inferior to DRV/r and EFV in virologic suppression\textsuperscript{1,2}
  – Superior to DRV/r in lipids
  – Superior to EFV in lipids; neuropsychiatric adverse events
  – Treatment emergent resistance uncommon (~1%)
  – No dose change in mild-mod liver disease; not studied in severe hepatic disease
  – DOR/TDF/3TC and DOR approved Aug 30 2018; once daily with or without food
  – Good choice in people for whom INSTI not optimal b/o side effects, drug interactions

Molina J-M et al, Lancet HIV 2018; Orkin C et al, CID 2018
WHO: Interim Guidance

BOX 1. RECOMMENDATIONS: FIRST-LINE ARV DRUG REGIMENS

1. A DTG based regimen may be recommended as a preferred first-line regimen for people living with HIV initiating ART (conditional recommendation)
   - Adults and adolescents (moderate-certainty evidence)
   - Women and adolescent girls of childbearing potential\(^a\) (very-low-certainty evidence)
   - Infants and children with approved DTG dosing\(^b\) (low-certainty evidence)
WHO: Note of Caution in those of child-bearing potential

• Exposure to DTG at the time of conception may be associated with NTD risk among infants.

• DTG appears to be safe when started after the period of risk of neural tube defects (i.e., up to 8 weeks after conception).

• Adolescent girls and women of childbearing potential who do not currently want to become pregnant can receive DTG together with consistent contraception (hormonal contraception and DTG have no reported or expected drug–drug interactions).

• An EFV-based regimen is a safe and effective first-line regimen and can be used among women of childbearing potential during the period of potential risk for developing NTDs.

• National programmes should consider the balance of benefits and risks when selecting the optimal ARV regimen for women and adolescent girls of childbearing potential (fertility levels, contraceptive availability and coverage, pretreatment resistance to NNRTIs at the population level, drug availability and the maternal and infant toxicity profile).
Are two ARVs as good as three?
Update on 2-drug therapy
NO NUKES
FROM THE MUSE CONCERTS • A NON-NUCLEAR FUTURE • MADISON SQUARE GARDEN • 1979
THE DOOBIE BROTHERS • JACKSON BROWNE
CROSBY, STILLS AND NASH • JAMES TAYLOR
BRUCE SPRINGSTEEN & THE E STREET BAND
CARLY SIMON • GRAHAM NASH • BONNIE RAITT
TOM PETTY & THE HEARTBREAKERS • RAYDIO
NICOLETTA LARSON • POCO • CHAKA KHAN
JESSE COLIN YOUNG • RY COODER • JOHN HALL
GIL SCOTT-HERON • SWEET HONEY IN THE ROCK
OR FEW
NRTI-limiting Regimens for Initial Therapy

• **LPV/r + 3TC (GARDEL)**
  – Non-inferior to LPV/r + 2 NRTI
  – Disadvantages: high pill burden, toxicities

• **DRV/r + RAL (NEAT001)**
  – Non-inferior to DRV/r + TDF/FTC
  – CD4 <200: DRV/r + RAL inferior to DRV/r + 2 NRTI
  – VL >100 K: more failures with DRV/r + RAL

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**DRV/r + 3TC for Initial Therapy**

- Randomized trial (ANDES)
  - DRV/r + 3TC (n=75)
  - DRV/r + 3TC/TDF (n=70)

- VL <50 at wk 48: 93 – 94%
  - Baseline VL >100K: high response rate

- Dual therapy non-inferior to triple therapy at wk 48

- Promising results; larger trial warranted

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**HIV RNA <50 (ITT)**

<table>
<thead>
<tr>
<th></th>
<th>3TC</th>
<th>3TC + tenofovir DF</th>
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</thead>
<tbody>
<tr>
<td>Overall (n=70/66)</td>
<td>93%</td>
<td>94%</td>
</tr>
<tr>
<td>Baseline HIV RNA &gt;100K Copies/mL (n=20/12)</td>
<td>91%</td>
<td>92%</td>
</tr>
</tbody>
</table>

**Difference (%):**

-1.0% (-7.5 ; 5.6%)

Figueroa et al, CROI 2018, Abstract 489
GEMINI 1 & 2: DTG + 3TC vs. DTG + TDF/FTC

Randomized, double-blind, parallel-group, multicenter, noninferiority studies

Screening (28 d) 1:1

Double-blind phase

Open-label phase

Continuation phase

DTG + 3TC (N=716)

DTG + TDF/FTC (N=717)

• ART-naive adults
• VL 1000-500,000 c/mL

Day 1  Week 24  Week 48  Week 96  Week 144

Eligibility criteria
• ≤10 days of prior ART
• No evidence of pre-existing viral resistance based on presence of any major resistance-associated mutation
• No HBV infection or need for HCV therapy

Primary endpoint at Week 48: participants with HIV-1 RNA <50 c/mL (ITT-E snapshot)^

Who was in GEMINI?
• % female: 14-16%
• African American: 11-14%
• VL >100K: 20-21%
• CD4 < 200: 8-9%

Cahn et al. AIDS 2018; Amsterdam. TUAB0106LB.
DTG + 3TC non-inferior to DTG + TDF/FTC

Virologic outcome

Adjusted treatment difference (95% CI)

GEMINI-1
- DTG + 3TC (N=356)
- DTG + TDF/FTC (N=358)

GEMINI-2
- DTG + 3TC (N=360)
- DTG + TDF/FTC (N=359)

Virologic success
- DTG + 3TC: 90%
- DTG + TDF/FTC: 93%

Virologic nonresponse
- DTG + 3TC: 4%
- DTG + TDF/FTC: 2%

No virologic data
- DTG + 3TC: 6%
- DTG + TDF/FTC: 5%

DTG + 3TC non-inferior to DTG + TDF/FTC with respect to proportion VL<50 at Wk 48 (snapshot, ITT-E population)

Based on Cochran-Mantel-Haenszel stratified analysis adjusting for the following baseline stratification factors: plasma HIV-1 RNA (≤100,000 c/mL vs >100,000 c/mL) and CD4+ cell count (≤200 cells/mm³ vs >200 cells/mm³).

Cahn et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.
GEMINI: Additional Results and Conclusions

• Results for 2-drug and 3-drug therapy comparable in those with VL > or <100K; lower response rate in 2-drug arm in those with CD4<200, but not virologic failure

• No resistance to INSTI or NRTI emerged in either arm (6 and 4 participants with virologic failure in 2D and 3D arms)

• DTG + 3TC: more favorable bone and kidney markers than DTG + TDF/FTC

• 2-drug option for those in whom ABC, TAF or TDF not optimal

• DTG/3TC for first line?
  • Paradigm shift
  • Need to know patient is NOT HBV infected before using
  • Longer term results eagerly awaited
Switching to NRTI-limiting regimens after virologic suppression (maintenance)

- LPV/r + 3TC/FTC (OLE)¹
- ATV/r + 3TC (SALT, ATLAS-M)²-³
- DRV/r + 3TC (DUAL)⁴
- DRV/r + RPV (small trial, n=60)⁵

- **DRV/r + DTG (DUALIS) – being studied**
- **DTG + 3TC (LAMIDOL, ASPIRE – favorable results⁶,⁷; TANGO – large RCT just launched⁸)**

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Switching to DTG + RPV in Virologically Suppressed Patients: SWORD-1 and -2

- Pts on stable 1\textsuperscript{st} or 2\textsuperscript{nd} ART (no change due to VF) and VL <50 for >12 mo.
- Randomized 1:1 to continue antiretroviral regimen (CAR) or switch to DTG + RPV
- DTG + RPV \textit{non-inferior} to CAR
- DTG/RPV single pill regimen available
- Food, acid lowering therapy, cation considerations

**Virologic outcomes at wk 48**

<table>
<thead>
<tr>
<th></th>
<th>DTG + RPV (n=513)</th>
<th>CAR (n=511)</th>
</tr>
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<tbody>
<tr>
<td>Virologic success</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>Virologic non-response</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>No virologic data</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
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Llibre JM et al. CROI 2017; Abstract 44LB.; Llibre JM et al, Lancet 2018
What are the options in someone who has difficulty taking daily drugs?

Long-acting agents in development
LATTE-2: Long-Acting Cabotegravir + Rilpivirine as Maintenance Therapy

Cabotegravir (integrase inhibitor) and rilpivirine (NNRTI): long-acting formulations\textsuperscript{1,2}

**LATTE-2: Phase 2a\textsuperscript{3}**

- **Open-label**
- ≥18 years of age
- ART-naïve
- CD4 ≥200
- Creatinine clearance ≥50
- No HBV or ALT ≥5x ULN

*In virologically suppressed patients, oral RPV added during last 4 weeks of induction phase

Qualification for maintenance phase: HIV RNA <50 between wk 4 and day 1.

**Baseline characteristics:**
- Median age: 35 years.
- Male: 92%.
- Median HIV RNA: 4.4 log\textsubscript{10} copies/mL.
- HIV RNA >100K copies/mL: 18%.
- Median CD4: 489 cells/mm\textsuperscript{3}.

1. Spreen HIV Clin Trials 2013;14:192
2. Spreen JAIDS 2014;67:481
### LATTE-2: Virologic Outcomes With LA Cabotegravir + Rilpivirine as Maintenance Therapy

#### Week 96 Results

**HIV RNA < 50 Copies/mL (%)**

- **Oral cabotegravir + 3TC/ABC daily (n=56)**: 84%
- **IM cabotegravir + IM rilpivirine**:
  - Every 4 weeks (n=115): 87%
  - Every 8 weeks (n=115): 94%
- **Success**:
  - 84%
  - 87%
  - 94%
- **Failure**:
  - 2%
  - 0%
  - 4%
- **No Virologic Data**:
  - 14%
  - 13%
  - 2%

- Protocol-defined virologic failure: q8 weeks (n=2 at weeks 4 and 48 [INI + NRTI resistance]) and oral cabotegravir (n=1 at week 8 [no resistance])

**Notes**:
- Injection site reactions: mild/moderate; transient
- High participant satisfaction
- Ongoing phase 3 trials (FLAIR, ATLAS): every 4-wk dosing; results in 2018
- ATLAS-2M: every 8-wk dosing; results in 2019

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Long-acting Cabotegravir + Rilpivirine: Stay Tuned!

ViiV Healthcare reports positive 48-week results for first pivotal, phase III study for novel, long-acting, injectable HIV-treatment regimen

ATLAS study meets primary endpoint, showing similar efficacy of a once-a-month, investigational, injectable two-drug regimen of cabotegravir and rilpivirine compared to a standard of care, daily, oral three-drug regimen

Full results from the study will be presented at an upcoming scientific meeting

15 August 2018
Long-acting NRTTI: MK-8591 (EFdA)

- Nucleoside RT translocation inhibitor (NRTTI)
- Half life of active anabolite: ≈80-130 hr
- Humans: single oral dose as low as 0.5 mg suppressed HIV RNA for >7 days

Phase 1b, single-dose, monotherapy study
Study population: ART naïve (N=30)

Change From Baseline HIV-1 RNA (log_{10} copies/mL)

Time (days)

MK-8591 0.5 mg
MK-8591 1 mg
MK-8591 2 mg
MK-8591 10 mg
MK-8591 30 mg

Grobler et al CROI 2017 #435
Matthews et al IAS 2017 #TUPDB0202LB
Long-acting NRTTI: MK-8591 (EFdA)

• Study in healthy volunteers: daily doses as low as 0.25 mg expected to lead to HIV suppression

• Phase 2b trial in people with HIV, in combination with doravirine (NNRTI) and 3TC, has started (DRIVE2Simplify)
  • Daily dosing

• Long half-life and its accumulation in tissues supports possible role in PrEP, long-acting implantable therapy

MK-8591 achieve target levels with only 0.25 mg dose

Matthews RP et al CROI 2018 #26
https://clinicaltrials.gov/ct2/show/NCT03272347
Markowitz M et al IAS 2017 #MOAX0203LB
Matthews RP et al CROI 2018 #26
Markowitz M et al CROI 2018, #89LB
New Medications for Multi-drug Resistant HIV - Phase 3 trials

• Ibalizumab
• Fostemsavir
HIV Entry Inhibitors

Slide courtesy of Trip Gulick, MD; Adapted from Moore JP, PNAS 2003;100:10598-10602.

* = FDA approved
Ibalizumab

- Humanized monoclonal Ab: binds CD4 on host cells; blocks HIV entry (post attachment inhibitor)\(^1\)
- Active against CCR5 and CXCR4 tropic HIV
- No cross resistance with other ARVs\(^2\)
- IV infusion: 2,000 mg loading dose then 800 mg every 2 wks
- Duration of infusion: 15-30 min

Approved in US for treatment of multi-drug resistant HIV on March 6, 2018

\(^1\)Emu B et al, Abstract 1686, IDWeek 2017; \(^2\)Weinheimer S et al, CROI 2018
Fostemsavir (FTR): Oral HIV Attachment Inhibitor

- Prodrug of temsavir: binds to gp120, inhibits HIV attachment to CD4
- Phase 3 trial in heavily treatment experienced patients with virologic failure (BRIGHTE)
- In those with only 1 or 2 ARV classes remaining, 54% who received FTR + optimized background regimen had VL <40 at wk 24
- In those with 0 ARV classes remaining, 36% who received FTR + OBR achieved VL <40

Virologic response through wk 24 (observed analysis)

"Regulatory submissions are currently anticipated to take place in the 2019/2020 timeframe"

Kozal M et al, 16th EACS, 2017

What’s On the Horizon

• Broadly neutralizing antibodies
• Other novel agents
HIV-1 antibody 3BNC117 suppresses viral rebound in humans during treatment interruption


Similar results with VRC01. Bar K et al, NEJM 2016
Combination bNAb, long-acting bNAb being studied for treatment, prevention, cure
Selected other investigational drugs in the pipeline:

- **Entry inhibitors**
  - fostemsavir
  - combinectin

- **NRTI s/NtRTI s (nukes)**
  - EFdA (MK-8591)
  - GS-9131

- **NNRTI s (non-nukes)**
  - doravirine
  - elvufavirine
  - rilpivirine LA

- **INIs (or INSTI s)**
  - bictegravir
  - cabotegravir
  - cabotegravir LA

- **Monoclonal antibodies (mAb)**
  - UB-421 (CD4 receptor)
  - ibalizumab (CD4 receptor)
  - PRO-140 (CCR5 receptor)

- **Protease inhibitor**
  - GS-PS1

- **Capsid inhibitor**
  - GS-CA1

- **Maturation inhibitor**
  - GSK3640254

HIV attaches to a CD4 cell.
HIV enters a CD4 cell and HIV proteins and enzymes are released into the cell.
Reverse transcriptase (RT) makes double strand HIV.
Integrate enables HIV to join the cell DNA.
Protease cuts and reassembles new HIV.
Each cell produces hundreds of new virions.
State of the ART: Take Home Points

• What are the current US and WHO Guidelines for treatment of HIV? → Most receive INSTI. Certain scenarios where other regimens may be preferred

• Are 2 ARVs as good as 3? → Promising data with DTG + 3TC (only if HBV neg)

• What are the options in someone who has difficulty taking daily drugs? Long-acting agents in development (LA CAB + RPV; MK-8591 or EFdA)

• What are new medicines for treating someone with multi-drug resistant HIV? → Ibalizumab (approved in US), fostemsavir (investigational)

• What’s on the horizon? → Broadly neutralizing Ab and others!