HIV Research
What's in the Pipeline?

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Initial Regimens: Recommended

INSTI based	▪ DTG/ABC/3TC; only if HLA-B*5701 negative (AI) ▪ DTG (QD) + TDF/FTC (AI) or TAF/FTC (AII) ▪ EVG/COBI/TAF/FTC ▪ EVG/COBI/TDF/FTC; only if pre-ART CrCl >70 mL/min (AI) ▪ RAL + TDF/FTC (AI) or TAF/FTC (AII)
PI based	▪ DRV/r (QD) + TDF/FTC (AI) or TAF/FTC (AII)

Note:
3TC can be used in place of FTC and vice versa; TDF: caution if renal insufficiency

So, what's wrong with these regimens?

- *Drug interactions*
  - Cobicistat and ritonavir
  - Gastric acid reducers (PPIs, H2-blockers) affect atazanavir and rilpivirine
- *Drug resistance still occurs*
  - Options for heavily treatment-experienced patients?
- *Side effects still potentially concerning*
  - Abacavir and cardiovascular disease?
  - CNS effects (e.g. sleep disturbances) with integrase inhibitors, e.g. dolutegravir?
  - What if first line agents are not tolerated?
  - Large STR pill size can be problematic for some patients
  - What are the long-term safety profiles of some newer drugs, like TAF?
- *Daily adherence and convenience still problematic for some patients*
  - Can we use smaller pills?
  - Is daily therapy required?
- *Cost can be a major determinant of regimen selection*
  - Can fewer drugs be used?

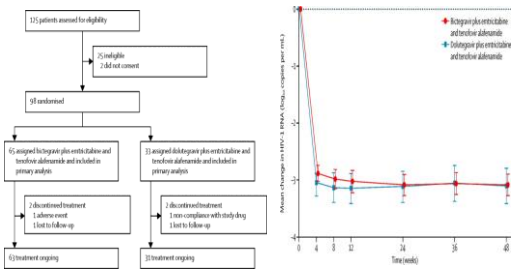
So what's in the pipeline?

- New drugs from existing classes
  - Bictegravir (INSTI)
  - Cabotegravir LA (INSTI) ± Rilpivirine LA (NNRTI)
  - Doravirine (NNRTI)
- New drugs from new classes
  - Fostemsavir (attachment inhibitor)
  - Ibalizumab (entry inhibitor)
- New strategies
  - Two drugs or three (is it heresy to even ask the question?)

Bictegravir

- New once-daily, unboosted INSTI
- Overcomes issues with cobicistat
- Can be co-formulated into an STR with FTC/TAF
- Maintains activity against patient-derived isolates with resistance to RAL, EVG, DTG

Bictegravir – Phase II Trial



Sax et al, Lancet HIV, 2017.

Bictegravir – Phase II Trial

	Bictegravir (n=65)	Dolutegravir (n=33)
Any adverse event	55 (85%)	22 (67%)
Diarrhoea	8 (12%)	4 (12%)
Nausea	5 (8%)	4 (12%)
Arthralgia	4 (6%)	2 (6%)
Fatigue	4 (6%)	2 (6%)
Headache	5 (8%)	1 (3%)
Chlamydial infection	4 (6%)	1 (3%)
Furuncle	3 (5%)	2 (6%)
Upper respiratory tract infection	5 (8%)	0
Back pain	4 (6%)	0
Flatulence	1 (2%)	2 (6%)
Gastroenteritis	1 (2%)	2 (6%)
Costochondritis	0	2 (6%)
Haemorrhoids	0	2 (6%)
Pruritus	0	2 (6%)

Sax et al, Lancet HIV, 2017.

Bictegravir – Phase II Trial

	Bictegravir (n=64)	Dolutegravir (n=32)
Any laboratory abnormality	28 (44%)	15 (47%)
Creatine kinase concentration elevation	8 (13%)	3 (9%)
AST concentration elevation	6 (9%)	1 (3%)
Serum glucose concentration elevation (fasting hyperglycaemia)	5 (8%)	4 (13%)
ALT concentration elevation	4 (6%)	0
LDL concentration elevation	4 (6%)	3 (9%)
Amylase concentration elevation	3 (5%)	2 (6%)
Haematuria	2 (3%)	2 (6%)
Glycosuria	1 (2%)	2 (6%)

Sax et al, Lancet HIV, 2017.

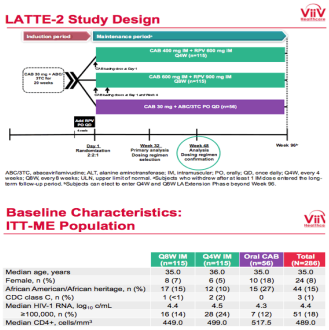
Bictegravir

- Currently in phase III trials (IU participating)
  - FTC/TAF/BIC vs. ABC/3TC/DTG
  - FTC/TAF + BIC vs. FTC/TAF + DTG
  - Week 48 data analysis underway, so stay tuned

Cabotegravir

- New long-acting INSTI with half-life of 3-7 weeks
- Can be formulated as an IM nanosuspension, thereby allowing for monthly injections
- Can be used with rilpivirine LA IM injections for HIV treatment
- May have useful activity as PrEP as monotherapy

Cabotegravir/Rilpivirine – LATTE-2



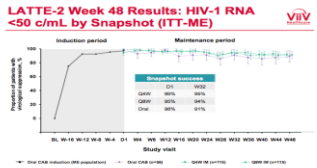
ABC/3TC, abacavir/lamivudine; ALT, alanine aminotransferase; IM, intramuscular; PO, orally; QD, once daily; Q4W, every 4 weeks; QW, every 8 weeks; ULN, upper limit of normal. *Subjects who withdrew after at least 1 IM dose entered the long-term follow-up period. †Subjects can elect to enter Q4W and QW LA Extension Phase beyond Week 96.

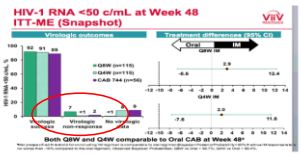
Baseline Characteristics: ITT-ME Population

	QW IM (n=115)	Q4W IM (n=113)	Oral CAB (n=56)	Total (N=284)
Median age, years	35.0	36.0	35.0	35.0
Female, n (%)	8 (7)	6 (5)	10 (18)	24 (8)
African American/African heritage, n (%)	17 (15)	12 (10)	15 (27)	44 (15)
CDC class C, n (%)	1 (<1)	2 (2)	0	3 (1)
Median HIV-1 RNA, $\log_{10}$ c/mL	4.4	4.5	4.3	4.4
≥100,000, n (%)	16 (14)	28 (24)	7 (12)	51 (18)
Median CD4+, cells/mm³	449.0	499.0	517.5	489.0

Margolis et al, IAS, 2016.

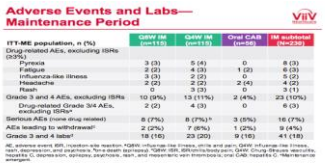
Cabotegravir/Rilpivirine – LATTE-2

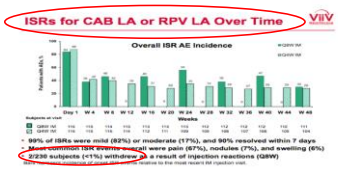




Margolis et al, IAS, 2016.

Cabotegravir/Rilpivirine – LATTE-2





Margolis et al, IAS, 2016.

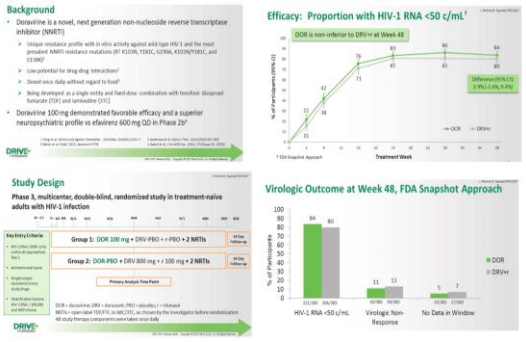
Cabotegravir

- Currently in phase II-III trials
  - FLAIR (phase III for HIV treatment; ongoing)
    - Compares oral ABC/3TC/DTG with monthly IM CAB LA + RPV LA (2 injections per month; each injection is 2mL)
    - There is a lead-in oral phase of 20 weeks with ABC/3TC/DTG and then an oral 4 week lead-in of CAB+RPV
    - RPV IM needs refrigeration
  - HPTN 083 (phase III for PrEP; ongoing)
    - Comparing CAB LA IM every 8 weeks (after 5 week oral lead-in) with daily FTC/TFV

Doravirine

- New once-daily NNRTI with in vitro activity against other NNRTI resistance mutations (K103N, Y181C, G190A, K103N/Y181C, E138K)
  - Resistance profile similar to RPV
  - DOR resistance does not affect RPV or EFV
  - Low potential for drug interactions
  - Fewer CNS effects than EFV in head-to-head trials
- Could be co-formulated with generic TDF and 3TC as an STR
- No food restrictions
- Can be given with acid-blocking agents

Doravirine – The DRIVE Trial



Molina et al, CROI 2017, Seattle.

Doravirine – The DRIVE Trial

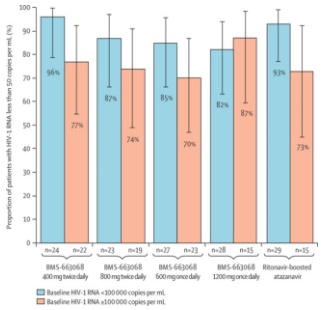
- Development of resistance mutations rare
  - None with DRV/r
  - Only 1 with DOR
- Adverse events similar, but fewer cases of diarrhea with DOR (14% vs. 22%) and better lipid profiles
- TDF/FTC/DOR vs. TDF/FTC/EFV and EFV to DOR switch trials ongoing

Fostemsavir

- HIV attachment inhibitor by blocking HIV gp120
- No cross-resistance to other entry inhibitors
- Not affected by tropism
- Perhaps not effective for HIV-2, subtype AE, group O
- Phase 2b trial evaluated various doses of fostemsavir in patients with first line failure (at least one week of ART experience previously), so early 'salvage'
  - Given with TDF and RAL
  - Comparison group was TDF+RAL+ATV/r

Lalezari et al, Lancet HIV, 2015.

Fostemsavir – Phase 2b Trial



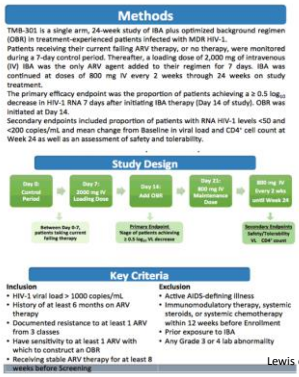
- Phase III Trial ongoing (IU participating)
  - Deep salvage
  - 600mg twice daily

Lalezari et al, Lancet HIV, 2015.

Ibalizumab

- Long-acting humanized IgG4 monoclonal antibody that blocks HIV entry into CD4 cells (new class of entry inhibitor) without interfering with normal immunologic functions
- Can block CCR5 and CXCR4 tropic viruses
- No known drug-drug interactions
- No known cross-resistance with other ART (including enfuvirtide)
- Half-life of ~3 days, so could be used every 1-2 weeks
- Infusion, not oral or IM

Ibalizumab Phase III Trial



Lewis et al, CROI 2017, Seattle.

Ibalizumab Phase III Trial

- 40 patients included, mean duration of HIV as 21 years, mean CD4 was 150, mean viral load of 100,287 (18% over 100,000), 43% required use of fostemsavir in OBR
- At Day 14
  - 83% had ≥0.5 $\log_{10}$ reduction in viral load vs. 3% in the control period
  - 60% had ≥1.0 $\log_{10}$ reduction in viral load vs. 0% in the control period

Lewis et al, CROI 2017, Seattle.

Ibalizumab Phase III Trial

- At Week 24
  - 83% and 48% had ≥1.0 and ≥2.0 $\log_{10}$ reductions in viral load
  - 43% had undetectable viral load <50c/mL
  - 50% had viral load <200c/mL
- No anti-IBA antibodies detected
- 17 SAEs reported in 9 patients
  - 4 deaths (liver failure, KS, AIDS, lymphoma)
- Currently under expedited FDA review

Lewis et al, CROI 2017, Seattle.

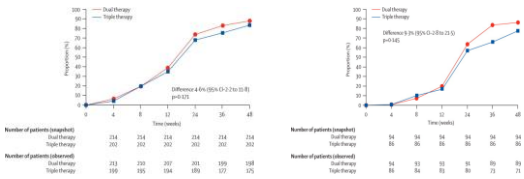
Two drugs vs. Three – Changing the Paradigm?

- Reducing the number of ART drugs in a regimen may be possible, *as long as the right combination is used*
  - Smaller pills
  - Might help preserve future drug options
  - Might help reduce costs
  - Might limit toxicities
- Most successful two-drug combinations were used as de-escalation strategies (switching from 3 drugs once viremia suppressed)
  - OLE (Switching from NRTI+3TC+LPV/r to just 3TC+LPV/r)
  - SALT (Switching from a 3 drug regimen to 3TC+ATV/r)
  - LATTE (Switching from 2 NRTI+CAB to CAB+RPV; IU participated)
  - SWORD 1 and 2 (Switching from PI, NNRTI, or INSTI + 2 NRTI to DTG+RPV)

Arribas et al, Lancet ID, 2015. Perez-Molina et al, J Antimicrob Chemother, 2017. Margolis et al, Lancet ID, 2015. Llibre et al, CROI 2017, Seattle.

Two drugs vs. Three – Changing the Paradigm

- But how about in ART-naïve?
- GARDEL showed that LPV/r+3TC BID was non-inferior to a 3 drug regimen of LPV/r+3TC BID plus another NRTI in ART-naïve patients



Cahn et al, Lancet ID, 2014.

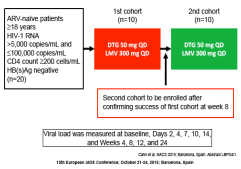
The PADDLE Trial

Objective

- To evaluate the antiviral efficacy, safety and tolerability of a dual therapy regimen with 3TC and DTG in HIV-1 infected, treatment-naïve individuals

PADDLE (Pilot Antiretroviral Design with Dolutegravir Lamivudine): Study Design

Phase IV, pilot, open-label, single arm exploratory trial



Stopping and Discontinuation Rules

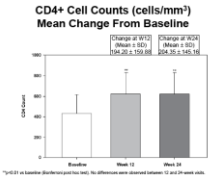
- Stopping rule
  - If at Week 8 more than 2 out of 10 patients show a viral load decrease <1 log the study will be discontinued
- Discontinuation criteria
  - Patients not achieving at least 1 log viral load reduction at Week 8 compared to baseline
  - Patients with viral load ≥1,000 copies/mL at Week 12
  - Patients with viral load ≥400 copies/mL at Week 24
  - Patients with a confirmed viral rebound (200 c/mL) after VL <50 c/mL

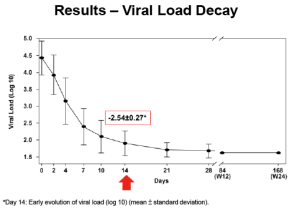
Baseline Characteristics

Baseline Characteristics	DTG/3TC n=20
Gender (male:female)	19/1
Age, years, median (IQR)	34 (31-43)
Mode of transmission (n) MSM Heterosexual	15 5
HIV RNA (copies/mL), median (IQR) *	24,129 (11,686-36,794)
CD4 count, cells/mm³, median (IQR)	507 (296-517)
CDC stage (%) A/B/C	90/10/0

Figueroa et al, EACS 2015, Barcelona.

The PADDLE Trial





*Day 14: Early evolution of viral load (log 10) (mean ± standard deviation).

Adverse Events at 24 Weeks

	Adverse Events possible related to DTG	
AE	Grade I	Grade II
Somnolence	1	
Epigastric pain	1	
Headache	2	1
Diarrhea	1	
Nausea	2	

All AEs were reported at the first week of treatment

No grade 3-4 laboratory toxicities were reported through 24 weeks
No SAE's reported

- GEMINI (phase III for ART-naïve; IU participating)
  - Comparing DTG+3TC with DTG+TDF/FTC
- Switch from TAF regimen to DTG+3TC

Figueroa et al, EACS 2015, Barcelona.

Other agents coming along….

- *Raltegravir SR (IU participated in its development)*
  - Might be co-formulated with doravirine for a nucleoside sparing regimen
- *Dolutegravir/rilpivirine STR*
  - 75mg tablet
- *Cenicriviroc*
  - CCR2/CCR5 fusion inhibitor
  - Could not only block HIV entry but also block inflammatory signals (CCR2 is the MCP-1 receptor) that might block neurocognitive impairment, cardiovascular disease, fatty liver disease
- *UB-421*
  - Another anti-CD4 monoclonal antibody
  - Weekly dosing
- *PRO 140*
  - CCR5 blocking antibody; works against maraviroc-resistant viruses
  - Weekly dosing

Wrap-up!!!

- Who can tell me which antiretrovirals are under development as injectable or infusable agents?
- Does bictegravir require a ‘boosting’ agent?
- What ‘salvage’ cases do you have that might benefit from these newer HIV medications?

Questions?

References

- Arribas et al, Lancet ID, 2015.
- Cahn et al, Lancet ID, 2014.
- Figueroa et al, EACS 2015, Barcelona.
- Lalezari et al, Lancet HIV, 2015.
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