UPDATES IN HIV THERAPEUTICS AND PREVENTION

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May 17, 2018

Agenda

- New Agents, Old Classes
- Novel Therapies
- Updates on long-acting ART
- Updates on dual therapy
- Updates on adverse events
- Prevention/Pre-Exposure Prophylaxis

This just in!

- Bictegravir/tenofovir alafenamide/emtricitabine

- Dolutegravir/rilpivirine

- Ibalizumab

New HIV drugs (from existing classes)

Doravirine

- NNRTI with fewer CNS adverse effects than EFV
- Can be used in the setting of the most common NNRTI resistance mutations (K103N, Y181C, G190A)
- DRIVE – phase III study
  - 766 participants randomized to 2 NRTIs + doravirine vs. 2 NRTIs + DVR/r
  - Doravirine was non-inferior to DRV/r at 48 weeks
  - Doravirine yielded a more favorable lipid profile than DRV/r

Molina JM et al. (Squires K presenting) *Doravirine is non-inferior to darunavir/r in phase 3 treatment-naïve trial at week 48.* Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle.

Doravirine

- **DRIVE-AHEAD**
  - Phase III study evaluating DOR/TDF/3TC vs TDF/FTC/EFV (*Atripla*®) in ART-naïve participants
  - DOR-regimen was non-inferior at 48 weeks
  - Fewer neuropsychiatric adverse events with DOR-regimen
- **DRIVE-SHIFT**
  - Phase III study evaluating switch from boosted PI-based regimen to DOR/TDF/3TC
  - Results pending

Squires KE, Molina JM, Sax PE, et al. Fixed dose combination of doravirine/lamivudine/TDF is non-inferior to efavirenz/emtricitabine/TDF in treatment-naïve adults with HIV-1 infection: week 48 results of the Phase 3 DRIVE-AHEAD study. 9th IAS Conference on HIV Science (IAS 2017), July 23-26, 2017, Paris. Abstract TUABO1043.

GS-9131

- NRTI – adenosine nucleotide analogue (like tenofovir)
- Prodrug, converted to active form in lymphocytes
- Minimal renal accumulation or potential for mitochondrial toxicity
- High barrier to resistance, not affected to common NRTI mutations (K65R, M184V, multiple TAMs)
- Low potential for drug-drug interactions

White KL et al. *GS-9131 is a novel NRTI with activity against NRTI-resistant HIV-1.* Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, abstract 436, 2017.

GS-PI1

- Novel **PROTEASE INHIBITOR**
- More metabolically stable than existing PIs, potentially can be dosed unboosted
- High in vitro barrier to resistance

Link JO et al. *Novel HIV PI with high resistance barrier and potential for unboosted QD oral dosing.*Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, abstract 433, 2017.

Novel drug therapies

MK-8591

AKA EFdA (4'-ethynyl-2-fluoro-2'-deoxyadenosine)

- Nucleoside reverse transcriptase translocation inhibitor (NRTTI)
- Half life of ~100 hours
- High (similar to TDF), long-lasting (>7 days) concentrations in rat lymphoid tissue, macaque rectal/vaginal tissue
- Parenteral formulation in rats detectable ~6 months
- Potential for use as less frequently-dosed PrEP or long-acting ART

Grobler J et al. *MK-8591 concentrations at sites of HIV transmission and replication.* Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, abstract 435. 2017.
Friedman E, et al. A single monotherapy dose of MK-8591, a novel NRTI, suppresses HIV for 10 days. In: Conference on Retroviruses and Opportunistic Infections (CROI 2016). Boston, Massachusetts; 201
Grobler J et al. *Long-Acting Oral and Parenteral Dosing of MK-8591 for HIV Treatment or Prophylaxis.* Conference on Retroviruses and Opportunistic Infections (CROI 2017), Boston, abstract 98. 2016.

MK-8591

- Mechanism of action:
  - Viral DNA incorporation, resulting in immediate chain termination
  - Structurally changes viral DNA, resulting in delayed chain termination
  - Binds to viral RNA primers, resulting in pair mismatch and chain termination

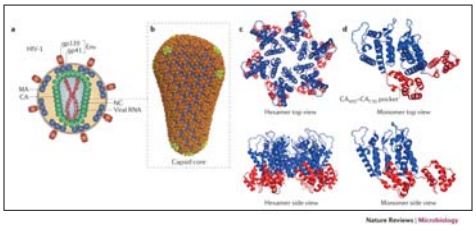
Merck letter 1543401, Accessed April 19, 2018

MK-8591

- Name that drug!

?

HIV Capsid Inhibitor



Nature Reviews | Microbiology

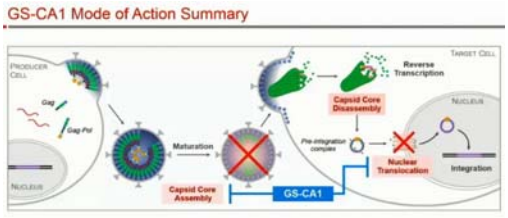
Pornillos, O., Ganser-Pornillos, B. K. & Yeager, M. Atomic-level modelling of the HIV capsid. *Nature* **469**, 424–427 (2011).

HIV Capsid Inhibitor

- GS-CA1
  - Capsid proteins self-assemble into hexamers, which assemble to form capsid core
  - GS-CA1 binds at interface of two adjacent molecules within a capsid hexamer
  - Interferes with capsid assembly, disassembly, and translocation of viral genetic material into nucleus

Tse WC et al. *Discovery of novel potent HIV capsid inhibitors with long-acting potential.* Conference on Retroviruses and Opportunistic Infections (CROI 2017). Seattle, abstract 38, 2017.

GS-CA1



Tse WC et al. *Discovery of novel potent HIV capsid inhibitors with long-acting potential.* Conference on Retroviruses and Opportunistic Infections (CROI 2017). Seattle, abstract 38, 2017.

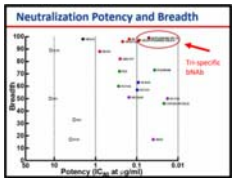
GS-CA1

- High barrier to resistance (and has HIV-2 activity)
- Very long half-life (in rats, a single parenteral administration maintained therapeutic plasma concentrations for >10 weeks)
- Monkey/human PK data are needed
- More potent than available ART

Tse WC et al. *Discovery of novel potent HIV capsid inhibitors with long-acting potential.* Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, abstract 38, 2017.

Broadly neutralizing Abs

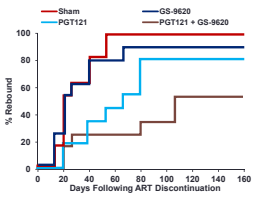
- Trispecific antibodies
  - Combination of 3 bNAs
  - VRC01, 10E8Va, PGDM1400 to target 3 HIV-1 epitopes
    - Combination maximized coverage and potency



Pegu, et al. Conference on Retroviruses and Opportunistic Infections, Boston, abstract 113LB, 2018.

Broadly neutralizing Abs

- PGT121
  - Broadly neutralizing antibody
    - In combination with GS-9620, a Toll-Like Receptor 7 Agonist
    - 44 SHIV-infected rhesus macaques on ART, randomized 1:1:1:1 to
      - PGT121
      - GS-9620
      - PGT121 + GS-9620
      - Placebo
    - ART was discontinued
    - 5/11 monkeys in PGT121 + GS-9620 group remained suppressed at 168 days, 6/11 demonstrated rebound, but then spontaneously began suppressing virus without ART
    - Adoptive transfer of PBMC and lymph node monocytes from aviremic monkeys did not induce SHIV infection in naïve recipients



bNAbs + innate immune activation may target the viral reservoir

Borducchi E, et al. *PGT121 COMBINED WITH GS-9620 DELAYS VIRAL REBOUND IN SHIV-INFECTED RHESUS MONKEYS.* Conference on Retroviruses and Opportunistic Infections (CROI) Boston, Massachusetts, March 4-7, 2018.

Long-acting ART

Cabotegravir LA

- INSTI
- Injectable depot formulation with an elimination half-life of 25–54 days
- Under investigation for both HIV treatment and prevention
- Phase II trial (ÉCLAIR) and HPTN 077 indicate dosing every 8 weeks
- New nano-formulated pro-drug NMCAB demonstrated 300x plasma drug levels at 6-8 weeks

Spreen W, et al. HIV Clin Trials. 2013;14(5):192–203

Markovitz M, et al. ÉCLAIR: Phase 2A Safety and PK Study of Cabotegravir LA in HIV-Uninfected Men. Presented at: CROI, February 22–25, 2016, Boston, Massachusetts

Zhou T et al. *A long-acting nanoformulated cabotegravir prodrug for improved antiretroviral therapy.*Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, abstract 439, 2017.

Rilpivirine LA

- NNRTI
- Injectable crystalline nanosuspension with plasma elimination half-life 44-61 days
- Under evaluation for HIV treatment (use in prevention remains indeterminate)

Verloes R, Deleu S, Niemeijer N, Crauwels H, Meyvisch P, Williams P. Safety, tolerability and pharmacokinetics of rilpivirine following administration of a long-acting formulation in healthy volunteers. HIV Med. 2015;16(8):477–84.

Cabotegravir LA + Rilpivirine LA

- LATTE-2:
  - CAB LA + RVP LA was non-inferior to EVF-containing 3-drug oral regimen
  - Administered every 4 or 8 weeks in ART-experienced participants
  - Sustained plasma drug levels up to 8 weeks

Margolis D et al. *Cabotegravir + rilpivirine as long-acting maintenance therapy: LATTE-2 week 48 results.* 21st International AIDS Conference, Durban, abstract THAB0206LB.

LATTE-2
Cabotegravir LA + Rilpivirine LA

- Background:
  - CAB LA + RVP LA was non-inferior to EVF-containing 3-drug oral regimen (LATTE-1)
- Methods
  - After 20-week induction on oral CAB/ABC/3TC, 286 participants randomized 2:2:1 to:
    - CAB LA 400mg/RPV LA 600mg Q 4 weeks
    - CAB LA 600mg/RPV LA 900mg Q 8 weeks
    - Continue daily oral CAB/ABC/3TC

Margolis DA, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. Lancet. 2017 Jul 21. pii: S0140-6736(17)31917-7

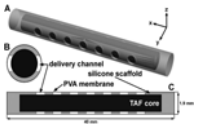
LATTE-2

- Results
  - Viral suppression at 96 weeks:
    - CAB LA 400mg/RPV LA 600mg Q 4 weeks – 87%
    - CAB LA 600mg/RPV LA 900mg Q 8 weeks – 94%
    - Continue daily oral CAB/ABC/3TC – 84%
  - Intermittent IM ART was non-inferior to oral therapy
  - >99% in IM groups reported satisfaction, 78% in oral group reported satisfaction with regimen

Margolis DA, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. Lancet. 2017 Jul 21. pii: S0140-6736(17)31917-7

Tenofovir alafenamide

- Due to aqueous solubility, unable to formulate as a nano-suspension
- More potent than TDF
- No side effects of bone loss or reduced renal function
- Formulation as subdermal implant in development
  - In vivo data on rabbits (N=6), which demonstrated therapeutic levels in PBMC for at least 70 days



Gunawardana M, Remedios-Chan M, Miller CS, Fanter R, Yang F, Marzinke MA, *et al.* Pharmacokinetics of long-acting tenofovir alafenamide (GS-7340) subdermal implant for HIV prophylaxis. *Antimicrob Agents Chemother* 2015;**59**:3913-3919.

Gatto G, et al. PHARMACOKINETICS OF TENOFOVIR ALAFENAMIDE BY SUBCUTANEOUS IMPLANT FOR HIV PrEP. Conference on Retroviruses and Opportunistic Infections, Boston,

Elsulfavirine

- Long-acting NNRTI, $T_{1/2}$ ~8 days
- Phase IIa, randomized, placebo-controlled trial comparing Elsufavirine + TDF/FTC (N=60) to EFV/TDF/FTC (N=60) in ART-naïve patients
- At 48 weeks, both regimens demonstrated viral and immunologic efficacy
- Elsulfavirine regimen was better tolerated
- Studies evaluating less frequent dosing are pending

Murphy R et al. *Elsulfavirine as compared to efavirenz in combination with TDF/FTC: 48-week study.*Conference on Retroviruses and Opportunistic Infections (CROI 2017). Seattle, abstract 452LB, 2017.

Other long-acting agents

- GS-CA1 (capsid inhibitor)
- Ibalizumab
- MK-8591

Dual therapy

Why dual therapy?

- Minimize toxicity
- Minimize drug-drug interactions
- Minimize pill/burden
- Optimize cost effectiveness

Dolutegravir + Rilpivirine

- **Fixed-dosed combination pill is now FDA-approved**

Dolutegravir + Lamivudine

- ACTG A5353
  - Pilot study on DTG/3TC in ART-naïve
  - 120 participants enrolled
  - 31% with HIV RNA >100,000 cpm
  - At 34 weeks, 96% achieved viral suppression (HIV RNA <50 cpm)

Two large trials currently pending to evaluate this regimen vs first line triple therapy regimens in treatment-naïve patients (GEMINI-1 and GEMINI-2)

Taiwo BO, et al. ACTG A5353: A pilot study of dolutegravir (DTG) + lamivudine (3TC) for initial treatment of HIV-1-infected participants with HIV-1 RNA >500,000 copies/ml. IAS 2017: Conference on HIV Pathogenesis Treatment and Prevention, Paris, France July 23-26 2017.

Dolutegravir + Lamivudine

- LAMIDOL
  - 104 treatment-experienced participants switched to dolutegravir + lamivudine
  - 101 maintained viral suppression at 40 weeks

Joly V et al. Promising results of dolutegravir + lamivudine maintenance in ANRS 167 Lamidol trial. Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, abstract 458, 2017.

And don't forget…

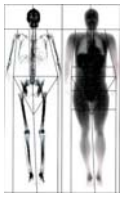
- Cabotegravir LA + rilpivirine LA (LATTE-2)

Margolis D et al. *Cabotegravir + rilpivirine as long-acting maintenance therapy: LATTE-2 week 48 results.* 21st International AIDS Conference, Durban, abstract THAB0206LB.

New (and old) adverse effects

Osteopenia/osteoporosis

- Tenofovir disoproxil fumarate (TDF)/Tenofovir alafenamide (TAF) **switch study** with low BMD
- 214 subjects with low BMD (T-score ≤ -2.0 at the lumbar spine, total hip or femoral neck) switched from TDF to TAF-containing regimen
- **At 96 weeks, BMD increased by 2.5% at lumbar spine and hip**
- Among 86 with baseline osteoporosis, **23% no longer met criteria**
- TDF to TAF switch may be an important treatment strategy in patients with high fracture risk



Brown T et al. *Switching from TDF to TAF in HIV-infected adults with low BMD: a pooled analysis.* Conference on Retroviruses and Opportunistic Infections (CROI 2017). Seattle, abstract 683, 2017.

Osteopenia/osteoporosis

- Zolendronate at time of ART initiation may **persistently** prevent bone loss
- 63 HIV+ participants randomized to zolendronate vs placebo at ART initiation
- Spine BMD remained 11% higher at 48 weeks in zolendronate arm, and 9-11% higher at 96 and 144 weeks

Ofotokun I, et al. Antiretroviral-induced Bone Loss is Durably Suppressed by A Single Dose of Zoledronic Acid. Conference on Retroviruses and Opportunistic Infections (CROI 2017).

Osteopenia/osteoporosis

- Switch from TDF to TAF
  - BMD recovery **augmented** with bisphosphonate
  - Among 214 HIV+ persons with osteopenia/osteoporosis switched from TDF to TAF
    - Concurrent bisphosphonate use associated with higher BMD in spine, but not hip, at 144 weeks

Brown TT et al. COMBINED EFFECTS OF BISPHOSPHONATES & TDF→TAF SWITCH IN HIV+ ADULTS WITH LOW BMD. Conference on Retroviruses and Opportunistic Infections (CROI), Boston, abstract 736, 2018.

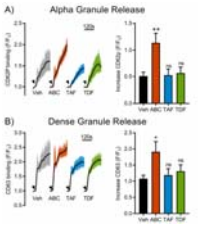
Lipodystophy

- Tesamorelin
  - Growth hormone-releasing hormone analogue
  - Increases visceral and subcutaneous fat density (smaller adipocytes, better quality)
  - 341 HIV+ participants randomized to tesemorelin vs placebo
    - Significant increase in fat density among tesamorelin group (as measured by Hounsfield Units), independent of fat quantity changes
    - Clinical significance remains under investigation

Lake JE, et al. TESAMORELIN IMPROVES FAT QUALITY INDEPENDENT OF CHANGES IN FAT QUANTITY. Conference on Retroviruses and Opportunistic Infections (CROI), Boston, abstract 736, 2018.

Cardiovascular disease

- Abacavir
  - *In vitro* collagen-evoked granule release enhanced by ABC, but not TDF or TAF, leading to platelet activation and aggregation
  - *In vivo*, ABC/3TC is associated with higher markers of platelet activity than TAF/FTC, which diminish when switched from ABC/3TC to TAF/FTC

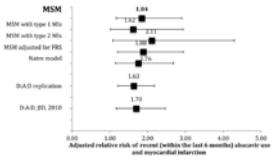


Taylor KA, et al. COMPARATIVE IMPACT OF ANTIRETROVIRALS ON HUMAN PLATELET ACTIVATION. Conference on Retroviruses and Opportunistic Infections (CROI), Boston, abstract 673, 2018

Mallon PW, et al. PLATELET FUNCTION UPON SWITCHING TO TAF VS CONTINUING ABC: A RANDOMIZED SUBSTUDY. Conference on Retroviruses and Opportunistic Infections (CROI), Boston, abstract 80, 2018

Cardiovascular disease

- NA-ACCORD
  - 29,077 person-years, 123 MI events
  - MI risk was greater for those who used ABC in previous 6 months [aHR = 1.84 (1.17–2.91)]



Elion et al. J Acquir Immune Defic Syndr Volume 78, Number 1, May 1, 2018

Dolutegravir

Less tolerable than we thought?

Dolutegravir

Neuropsychiatric side effects

- Significant CNS adverse effects
  - Insomnia, dizziness, headache, paresthesias, poor concentration, depression

	Discontinuation due to any adverse event (12-month rate)	Discontinuation due to neuropsychiatric event (12-month rate)
Dolutegravir	7.6%	5.6%
Elvitegravir	7.6%	0.7%
Raltegravir	3.3%	1.9%

Among 985 patients who started dolutegravir, 49 stopped due to neuropsychiatric adverse effects.

Neuropsychiatric AEs leading to discontinuation more frequently seen in:
- Women (HR = 2.64; 95% CI, 1.23-5.65, p = 0.012)
- Age >60 years (HR = 2.86; 95% CI, 1.42-5.77, p = 0.003)
- DTG + ABC (HR = 2.42; 95% CI, 1.38-4.24, p = 0.002)

Quercia R et al. *Psychiatric adverse events from the DTG ART-naive phase 3 clinical trials.* International Congress on Drug Therapy in HIV Infection (HIV Glasgow), Glasgow, abstract P210, 2016.
Sabranski M et al. *Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients.* International Congress on Drug Therapy in HIV

Dolutegravir
Neuropsychiatric side effects

- The Quintiles IMS database (pharmacy and medical claims records)
- 54,151 HIV+ patients on DTG, EVG, RAL (2006-2016)
- Outcomes: insomnia/sleep disturbance, depression
- Insomnia/sleep disturbance events
  - significantly higher for patients treated with DTG vs EVG (IRR 1.21 [95% CI 1.09-1.33, p<0.001]), but not DTG vs RAL
- Incident depression
  - significantly higher for patients treated with DTG vs EVG (IRR 1.18 [95% CI 1.09-1.27, p <0.001]), but not DTG vs RAL

Wohl D, et al. Selected CNS outcomes among INSTI antiretrovirals. IDWeek, San Diego, 2017

Dolutegravir
Neuropsychiatric side effects

OPERA cohort

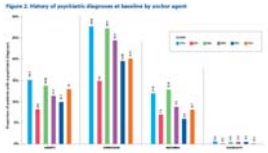
- 11539 HIV+ participants who received DTG, RAL, EVG, EFV, RPV, DVR between 1/2013 – 8/2015
- No significant differences in incident psychiatric disorders between participants taking DTG and participants taking any of the other drugs

Drug	Drug discontinuation ≤14 days after incident psychiatric disorder diagnosis (%)	p-value (reference: DTG)
DTG	0.3	--
RAL	1.7	p<0.001
EVG	0.8	p=0.04
EFV	2.2	p<0.001
RPV	1.0	p=0.006
DRV	1.0	p=0.006

Hsu R, et al. Psychiatric Disorders Observed in HIV+ Patients Using 6 Common 3rd Agents in OPERA. CROI 2017 Feb 14-16 Seattle, WA

Dolutegravir
Neuropsychiatric side effects

- OPERA cohort
  - Baseline anxiety more likely in participants on DTG than EFV, DRV, or RPV (all p<0.001).
  - Baseline depression more likely in participants on DTG than EFV, RPV, or EVG (all p<0.0001).
  - Baseline insomnia more likely in participants on DTG than EFV, DRV, RPV, or EVG (all p<0.0001).



Hsu R, et al. Psychiatric Disorders Observed in HIV+ Patients Using 6 Common 3rd Agents in OPERA. CROI 2017 Feb 14-16 Seattle, WA

Dolutegravir
Weight gain

- 495 HIV+, virally suppressed patients on EFV/TDF/FTC at VUMC
  - 136 switched to INSTI-containing regimen
    - 58 containing DTG
    - 21 containing RAL
    - 42 containing ELV
  - 34 switched to PI-containing regimen
  - 325 remained on EFV regimen
- Those switched to INSTI-containing regimen gained significantly more weight at 18 months than those that stayed on initial regimen
  - +2.9kg vs +0.9kg, p=0.003
  - Non-significantly higher weight gain among DTG group (+5.3kg) vs RAL/ELV group (+2.8kg)

Norwood J, et al. Weight Gain in Persons with HIV Switched from Efavirenz-based to Integrase Strand Transfer Inhibitor-based Regimens. J Acquir Immune Defic Syndr. 2017 Aug 18

Pre-Exposure Prophylaxis

Pre-Exposure Prophylaxis

- Out of 1.2 million individuals at high risk for HIV
  - 136,000 are receiving TDF/FTC
    - Up from 80,000 the previous year

Mera R, et al. Truvada (TVD) for HIV pre-exposure prophylaxis (PrEP) utilization in the United States (2013-2015). Presented at: AIDS 2016. Durban, South Africa. July 18-22. 2016

Mera R, et al. Changes in Truvada® for HIV Pre-exposure Prophylaxis Utilization in the USA: 2012-2016 – Disparities. 10th IAS Conference on HIV Science. 23-26 July 2017. Paris, France.

Smith D, et al. MMWR Morb Mortal Wkly Rep 2015;64:1-8

Tenofovir Alafenamide (TAF)?

- Achieves high intracellular concentrations, but lower plasma and tissue concentrations than TDF
  - 13-fold lower than TDF in rectal tissues
  - 11-fold lower than TDF in cervicovaginal fluid

Due to low plasma and tissue concentrations, TAF's use in PrEP is uncertain

Garrett KL, et al. **Concentrations of TFV and TFVdp in Female Mucosal Tissues After a Single Dose of TAF.** Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, Abstract 102LB, 2017.

Tenofovir Alafenamide (TAF)?

- However…
  - An animal study suggests efficacy
    - 6 macaques received TAF/FTC before and after rectal weekly exposure of SHIV or up to 19 weeks
    - 6 macaques received placebo
    - None of the 6 receiving TAF/FTC acquired SHIV, while all 6 receiving placebo did
  - A more recent, similar study with female pigtail macaques demonstrated 82% efficacy after vaginal exposure to SHIV.

Massud I, et al. Chemoprophylaxis with Oral FTC/TAF Protects Macaques from Rectal SHIV Infection. Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, Abstract 107, 2017.

Massud I, et al. CROI 2018. Boston, MA. Oral 85

DISCOVER Trial

- "A Phase 3, Randomized, Double-blind Study to Evaluate the Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex With Men and Are At Risk of HIV-1 Infection"
- Comparison of efficacy of TAF+FTC vs TDF+FTC
- Estimated completion: September 2020

https://clinicaltrials.gov/ct2/show/NCT02842086

Cabotegravir LA

- Integrase inhibitor with long half-life
- Long acting, depot-controlled nanosuspension has an even longer half-life (25-54 days)
- Use as PrEP in phase 2 trials:
  - Oral lead-in
  - Will likely need every 2 months (6 injections/year)
  - Injection site reactions common
  - Most patients still preferred this over daily oral PrEP

Markovitz M, et al. ECLAIR: Phase 2A Safety and PK Study of Cabotegravir LA in HIV-Uninfected Men. Presented at: CROI, February 22–25, 2016, Boston, Massachusetts

Rilpivirine LA

- MWRI-01 trial
  - 8 women and 4 men randomized to varying doses (600mg, 1200mg, or 1200mg at 0 months, 2 months, 4 months)
  - Ex vivo explant infection model
    - Rectal tissue: infection inhibited 4 months after last injection
    - Cervical tissue: infection inhibited 2 months after first injection

McGowan I, et al. An Open Label Multiple Dose Phase 1 Assessment of Long Acting Rilpivirine - Long-Acting Rilpivirine Suppresses Replication in Rectal Explants. 19th IAS Conference on HIV Science (IAS 2017), July 23-26, 2017, Paris

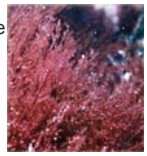
MK-8591

- Nucleoside reverse transcriptase translocation inhibitor (NRTTI)
- High, long-lasting (>7 days) concentrations in rat lymphoid tissue, macaque rectal/vaginal tissue
- Weekly dosing with MK-8591 (N=8) vs placebo (N=8) in macaques
  - All subjected to repeated intra-anal exposure to SHIV
  - After 12 weeks, all in control group were infected with SHIV, 0 in MK-8591 group were infected

Grobler J et al. *MK-8591 concentrations at sites of HIV transmission and replication*. Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, abstract 435, 2017.

Markowitz M. Weekly Oral MK-8591 Protects Male Rhesus Macaques against Repeated Low Dose Intrarectal Challenge with SHIV159CP3 . 9th IAS Conference on HIV Science (IAS 2017), July 23-26.

Griffithsin



- Red algae-derived protein with glycans demonstrating high affinity to viral envelope proteins
- Potent HIV-1 entry inhibitor
- Synergistic activity when combined with carrageenan (a seaweed polysaccharide)
- As a vaginal insert, 80% protection from SHIV challenge in rhesus macaques
  - 8/10 in drug group
  - 0/10 in placebo group

Derby N, et al. GRIFFITHSIN/CARRAGEENAN INSERTS PREVENT SHIV, HSV-2, AND HPV INFECTIONS IN VIVO. Conference on Retroviruses and Opportunistic Infections (CROI).

STI Prophylaxis

- Among participants in IPERGAY
  - 232 randomized to doxycycline 200mg PO x1 up to 72 hours after sex vs. placebo
  - After median 8.7 month follow-up
    - 70% (7 vs. 21) fewer chlamydial infections in doxycycline arm
    - 73% (3 vs. 10) fewer syphilis infections in the doxycycline arm
    - No effect on gonorrhea (22 infection in doxycycline arm, 25 in control arm)

Molina J-M et al. *On demand post exposure prophylaxis with doxycycline for MSM enrolled in a PrEP trial.* Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle.

- PARTNER
  - European prospective study of ~900 sero-discordant partners in which the HIV+ partner is undetectable, representing 58,000 condomless sex acts
  - No transmissions were observed.
- OPPOSITES ATTRACT
  - prospective study from Australia, Thailand and Brazil of 343 gay, sero-discordant partners representing 12,000 condomless sex acts.
  - No transmissions were observed.

Rodger AJ, et al. Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy JAMA. July 2017

Bavinton B, Grinsztejn B, Phanuphak N, et al. HIV treatment prevents HIV transmission in male serodiscordant couples in Australia, Thailand and Brazil. 9th IAS Conference on HIV Science (IAS 2017), July 23-26, 2017, Paris.

Thank you!

Questions?