Women and vulnerable populations

HIV in Women's Workshop & CROI Feedback 2023

Yvonne Gilleece

HIV and STIs in women
Ruanne Barnabas

- Globally only 15-20% of WAYG eligible for HPV vaccination have been vaccinated vs WHO goal of 90%
- GC/Syphilis increase risk of HIV acquisition x5-6,
- HSV2/Chlamydia/MGen increase risk of HIV acquisition x2
- HIV is associated with increase risk STI exposure including in pregnant women
- GC/Chlamydia x1.8
- TV x 1.54
- MGen x 1.7
- HPVx2-3

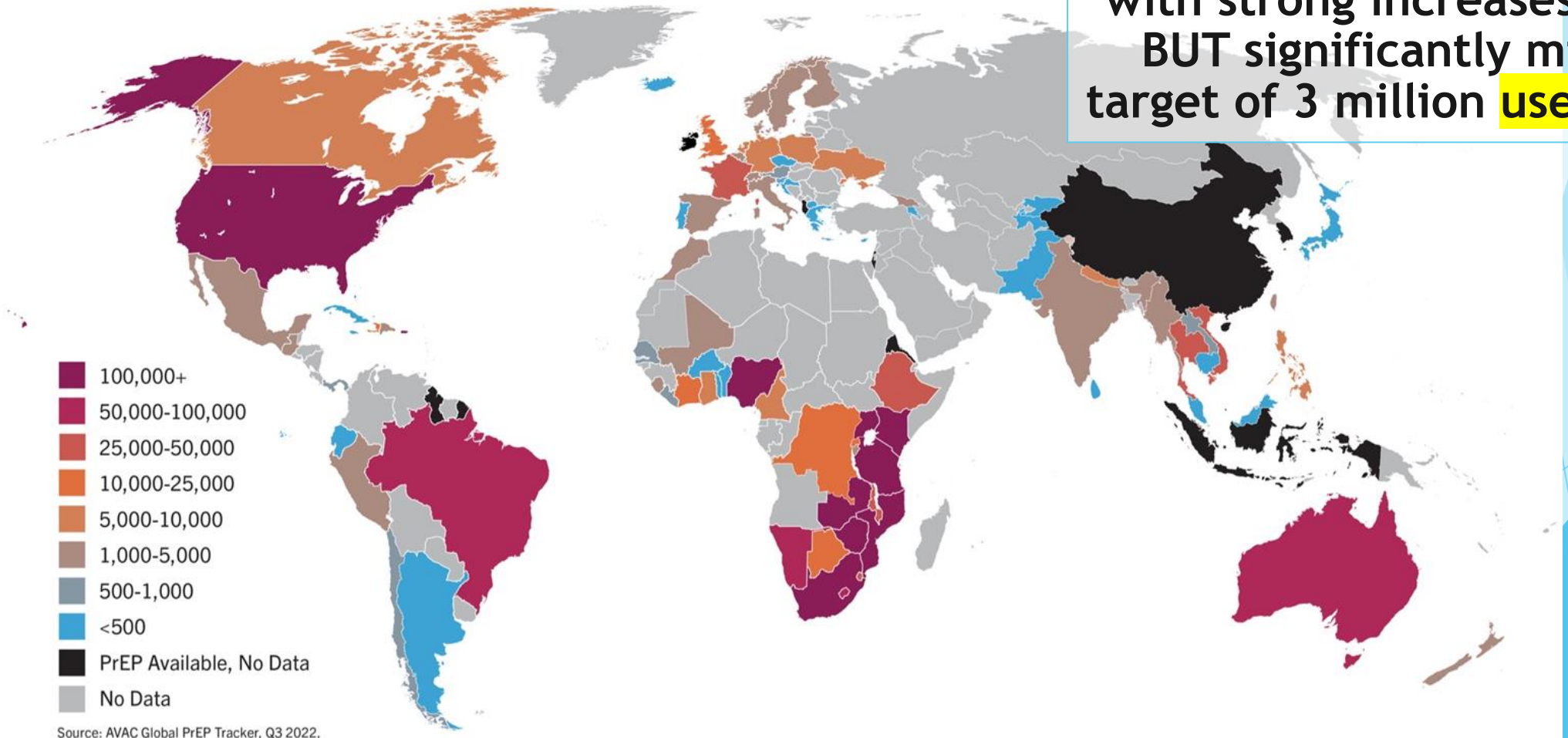
Improving recruitment of Black women to health related research, Amber Sophus

- US poor history of research in black women, Tuskagee etc
- What makes an ad good ie effective. Visual appeal, include your target population. Access to something free or something new
- FGD from which ads for PrEP were developed, n=10 (5x2)
- 301 looked at ads, went online to learn more
- 34yo (18-70), 85% non Hispanic. Liked the ad with younger women more. Ad seen on FB most commonly. Liked women of colour, messaging, diverse but positive images. Diverse age and skin tone preferred. Like a call to action headline.
- Use of social media then created the problem of knowing who was real and who was bot

PrEP and contraception combined, Mitchell Warren, AVAC

Global PrEP 10 years in

Approx. total PrEP initiations:
3.8 million
with strong increases in 2022 -
BUT significantly missed UN target of 3 million users by 2020



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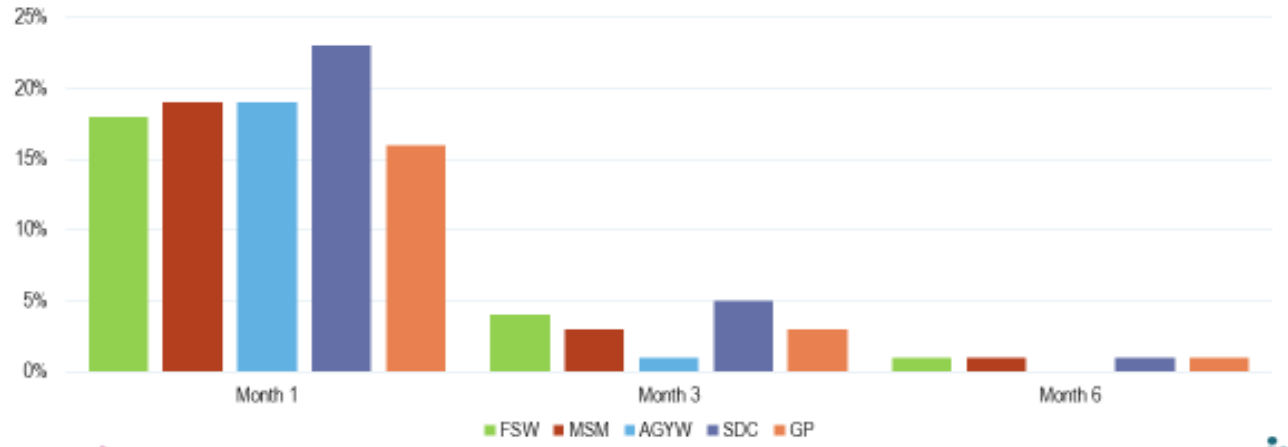
But Initiation ≠ Use ≠ Impact

PrEP continuation rates tend to decline significantly by 3 months after initiation across all populations[1]

Study	Country	Continuation Rates (M=month)
POWER[2]	Kenya, South Africa	43% (M1); 20% (M3)
PrIYA[3]	Kenya	MCH Clinic: 39% (M1); 12% (M6) FP Clinic: 41% (M1); 24% (M3); 15% (M6)
EMPOWER[4]	South Africa, Tanzania	73% (M1); 61% (M3); 34% (M6)

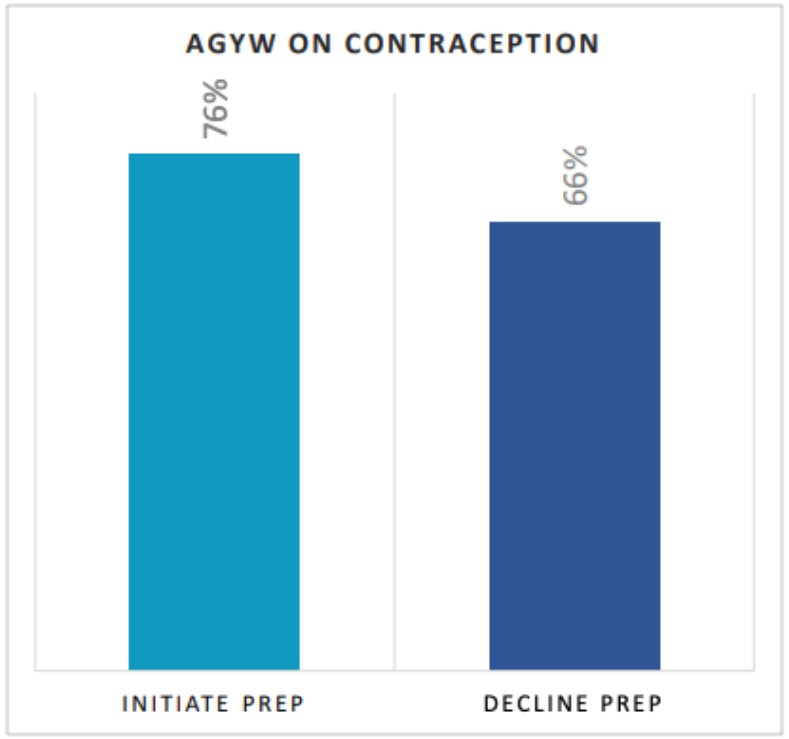
Lesson 1: Continuation Rates are Low and Vary by Population Type [5]



Source: [1] Rodrigues et al., Starting and staying on PrEP: a scoping review of strategies for supporting and improving effective use of PrEP, HIV R4P (2021); [2] Rousseau-Jemwa et al., Early Persistence of HIV Pre-exposure Prophylaxis (PrEP) in African Adolescent Girls and Young Women (AGYW) from Kenya and South Africa, HIV R4P (2018); [3] Kinuthia et al., Pre-exposure prophylaxis uptake and early continuation among pregnant and post-partum women within maternal and child health clinics in Kenya: results from an implementation programme (2019); Mugwanya et al., Integrating preexposure prophylaxis delivery in routine family planning clinics: A feasibility programmatic evaluation in Kenya (2019); [4] Delany-Moretlwe et al., Empowerment clubs did not increase PrEP continuation among adolescent girls and young women in South Africa and Tanzania - Results from the EMPOWER randomised trial, AIDS 2018 (2018); [5] Jilinde (2019).

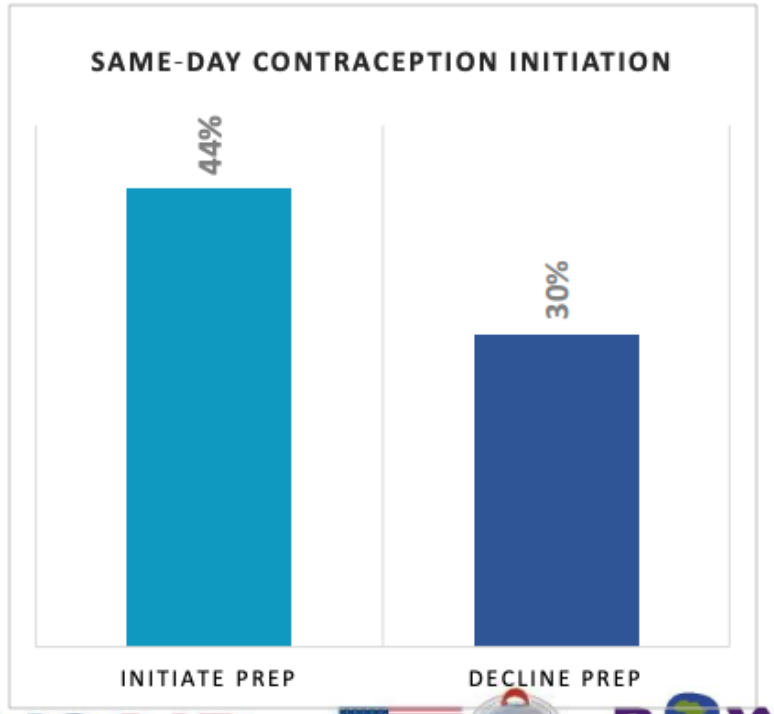
Potential for Oral PrEP and FP Initiation

Young women using contraception were more likely to initiate PrEP on the same day (p=0.001)



POWER project, Uptake of PrEP and hormonal contraception

PrEP initiation was significantly associated with contraception initiation on the same day (p=0.003)



USAID FROM THE AMERICAN PEOPLE

PEPFAR

POWER

Rousseau E, Baeten JM, Morton J, et al. (2019). http://regist2.virology-education.com/presentations/2019/13INTEREST/24_Rousseau.pdf ; Pleaner, M. et al. (2021). https://doi.org/10.3389/frph.2021.684114; Mugwanya K. K., Pintye, J., Kinuthia, J. et al. (2019). https://doi.org/10.1371/journal.pmed.1002878.

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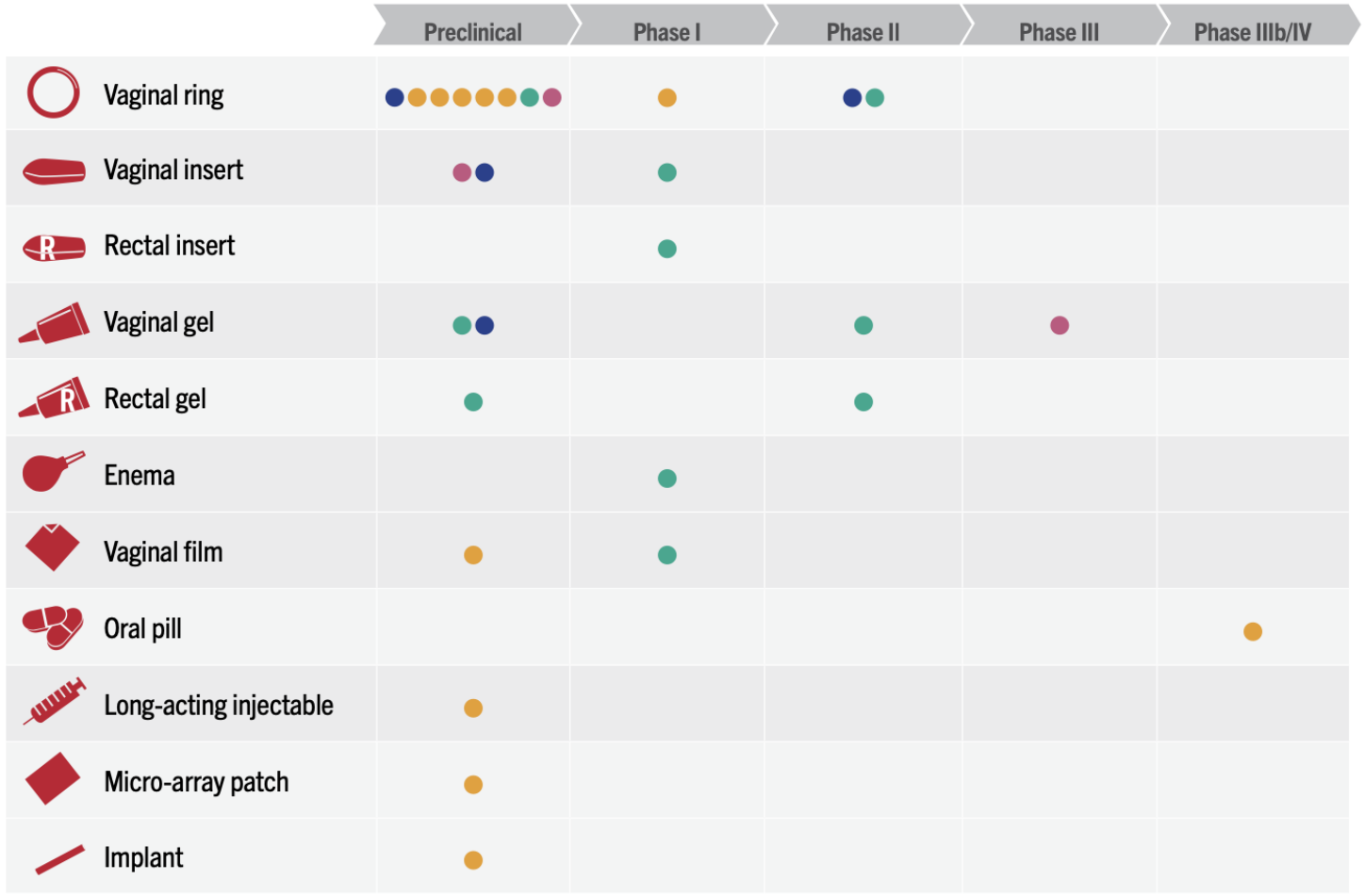
Product Pipeline Overview



HIV + other STIs	HIV + other STIs + Contraception	HIV + Contraception	Contraception + other STIs
10	4	11	3

Advocates' Guide to Multipurpose Prevention Technologies, AVAC, 2021

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The Dual Prevention Pill (DPP)

- Viatris developing **co-formulated tablet with 28-day regimen** (TDF/FTC, oral PrEP + LNG/EE, combined oral contraception (COC))
- **Different color pills** for 21 vs. 7 days (dark pink and light peach, respectively)
- **Packaging will be wallet pack** with tear-off weekly sheets with instructions on them
- Pill color, packaging, brand names **validated with women**
- **Branding/secondary packaging** will have women's lifestyle feel

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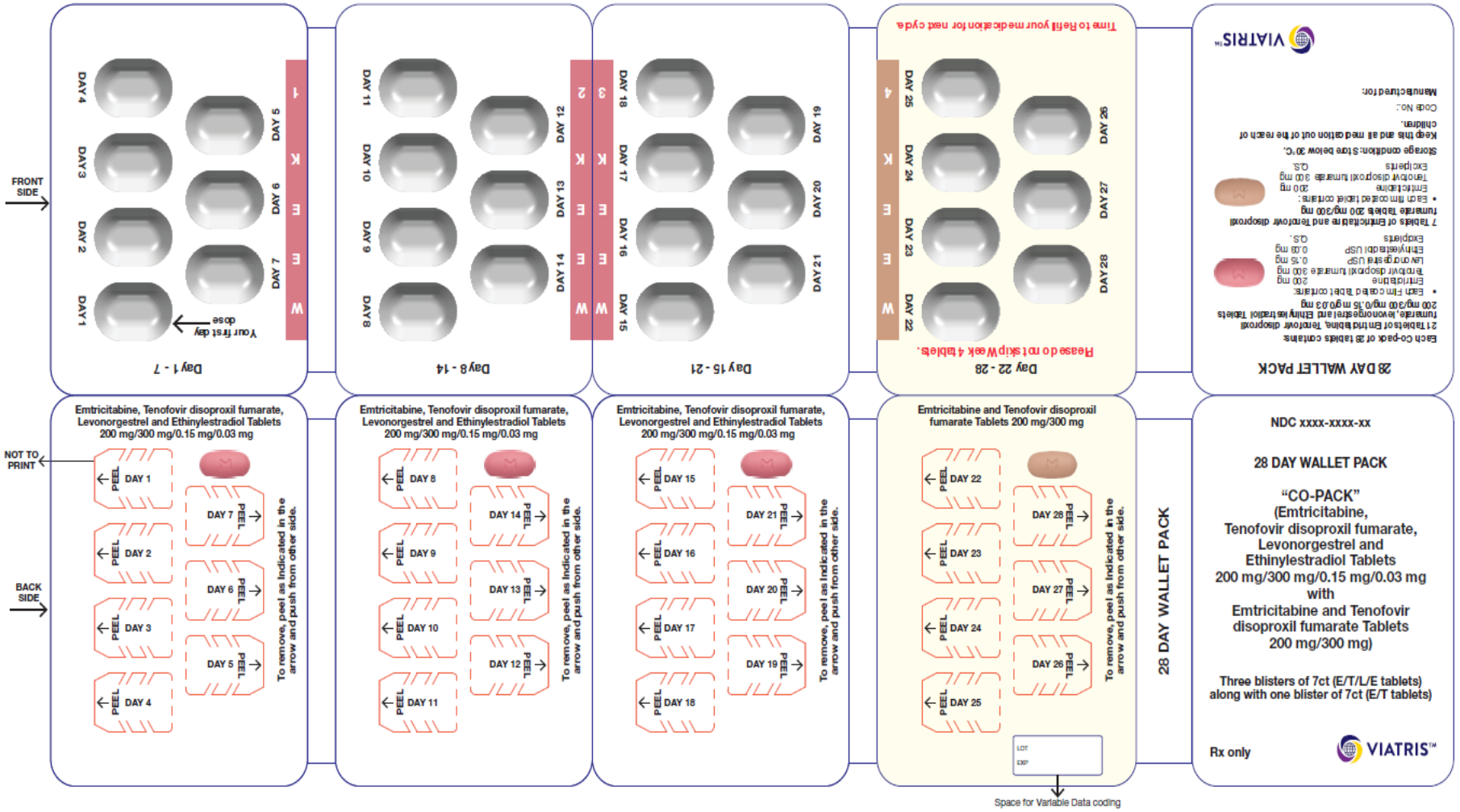
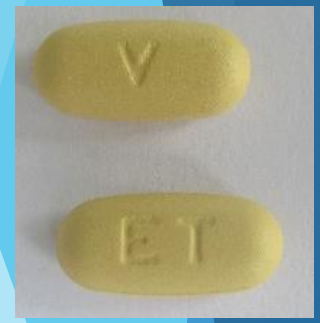
The Dual Prevention Pill (DPP)

Illustrative mock-up of DPP packaging by Viatris



Proposed DPP tablet colors



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Potential for the DPP

Possible Upsides

- Dual protection
- Reduce stigma of "PrEP pill"
- Simplify user experience
- Blister-pack replaces "rattling bottle"
- Would be 1st MPT since 1993 approval of the female condom, and first that includes PrEP to lay foundation for next-gen products

Possible Downsides

- Still a large pill – until we know more about F/TAF
- Method switching from long-acting reversable contraception
- Still relies on daily adherence
- Not an injectable, and in various studies, often stated preference for injectable MPT

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DELIVER HPTN042
DPV and oral PrEP during pregnancy

- A safety study enrolling pregnant people and their infants
- Developing countries. Community engagement from the start
- Three cohorts according to age
- 36-38, 30-35, 12-29 starting with latest pregnant first for safety, until 6 weeks post partum
- PO PrEP vs DPV ring 1:1
- Most common outcome full term live birth
- Gestational HTN most common problem
- No HIV transmissions, 0 maternal death, 2 unrelated infant deaths
- Returned rings and dbs TDF levels show drugs used
- Excellent retention with >95% appt attendances

OA4 Dynamic choice of HIV PrEP in women attending Antenatal clinic in Kenya

- RCT offering PEP/PrEP support/different venues for follow up
- >15yo HIV neg
- 48 week follow up of self reported PEP/PrEP use
- 6% previous PEP/PrEp use at baseline
- Better uptake 70% vs 28% in those offered intervention with support vs control (usual ANC support)
- Majority chose PrEP (vs PEP)100% at beginning but this fell down to 75% by 48w
- 11% chose PEP at least once
- Number not using either increase over time
- Self testing increased from 34% to 54%

Clinic experience increasing PrEP awareness (O&G), Runzhi Wang

- Pregnant women with positive STI
  - Phase 1
    - PrEP education
    - Nurse counselling
  - Phase 2
    - Clinical decision support tools
    - PrEP to counsel and start PrEP or not
  - Phase 3: RCT n=218 each arm
    - Young, Hispanic, single, 50% previous drug use (marijuana)
    - If seen by PrEP nurse prep was discussed in 66% vs 12%
    - Effective while study was in progress but benefit evaporated at study end
    - Plan is to have educational highlights and promotion ongoing

Steatosis & Fibrosis in WLWH switching to INI use

- Background: Steatosis prevalence is 25% in population living with HIV
- Women experience more weight gain with INSTI
- WIHS cohort, on ART >2y, VL<200, often switching from PI/NNRTI
- 60% no alcohol, excluded if >12u per week
- Steatosis: CAP >248
- Fibrosis FS >7.1kPA
- Predictor of steatosis: FAST score >0.67)CAP/FS/AST)

Lahari, et al. CROI Seattle 2023

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Results

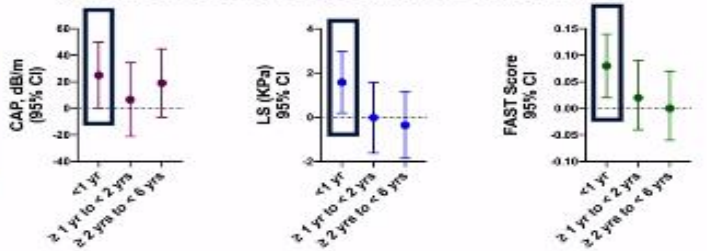
Cohort Characteristics (time of FibroScan)		
Mean (SD), median (Q1, Q3) or n(%)	INSTI N=123	Non-INSTI N=134
Age, yrs	50 (8)	49 (8)
Black race	82 (67)	107 (80)
Alcohol use		
Abstainer	75 (62)	84 (63)
1-7/wk	44 (36)	49 (37)
CD4, cells/mm³	836 (316)	758 (290)
CD4 nadir	214 (87, 344)	245 (141, 360)
NRTI		
TDF*	28 (23)	109 (81)
TAF*	51 (42)	15 (11)
ABC*	33 (27)	10 (8)
BMI, kg/m²	32 (8)	32 (8)

*p<0.001

Change from pre-switch to Fibroscan

	INSTI	Non-INSTI
Weight, kg	+2.4 (7.9)	+1.6 (7.8)
BMI, kg/m²	+0.95 (3.0)	+0.6 (2.9)
Waist circumference, cr	+1.5 (7.6)	+0.6 (6.9)

Differences in measures of Hepatic Steatosis, Fibrosis, and FAST Scores between INSTI & Non-INSTI



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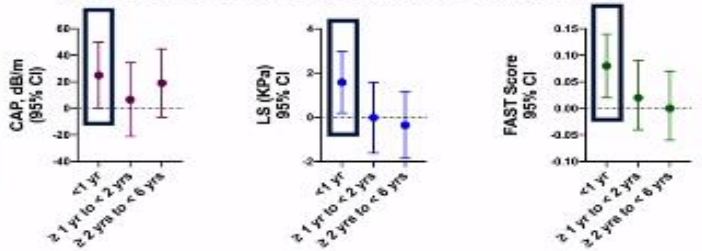

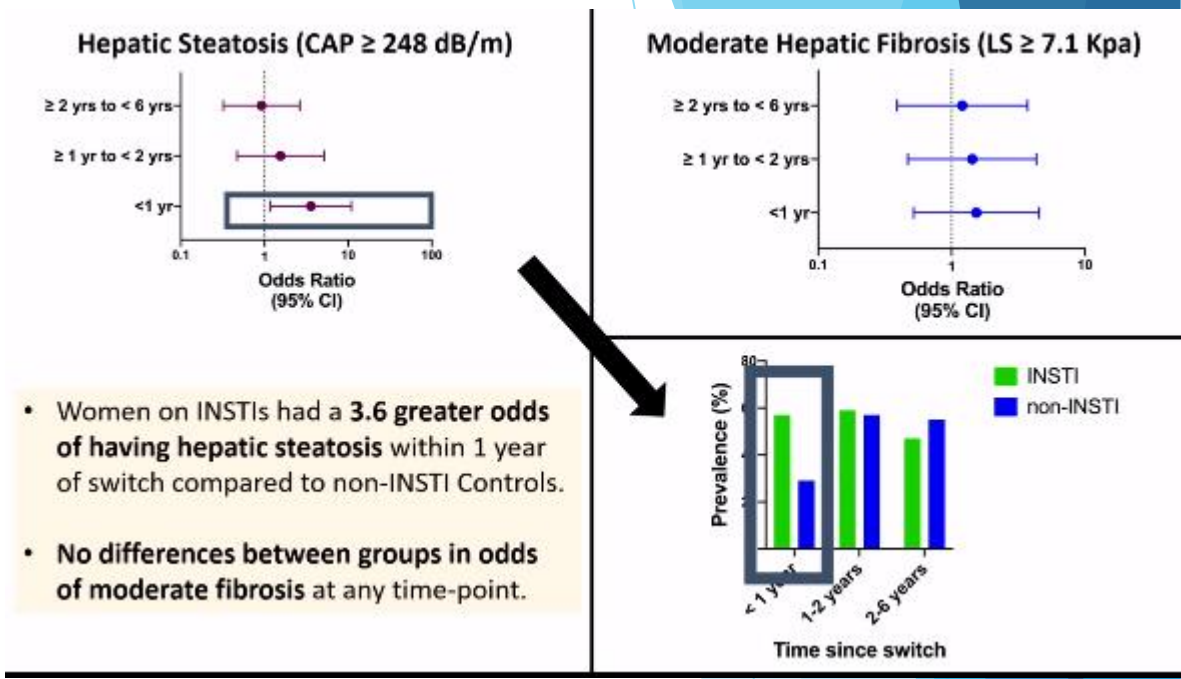

- Women on INSTIs had a **3.6 greater odds of having hepatic steatosis** within 1 year of switch compared to non-INSTI Controls.
- **No differences between groups in odds of moderate fibrosis** at any time-point.

Lahari, et al. CROI Seattle 2023

Sex differences for Metabolic Dysfunction Associated Liver Disease (MAFLD)

- Background: PLWH higher risk of MAFLD
- In non HIV population MAFLD – higher steatosis in men but higher fibrosis in women
- Alcohol – 40% had >10 unit per week
- Steatosis CAP >270 plus BMI >25/T2DM
- Fibrosis LSM>8
- Age 52, 25% female

Kablawi et al. CROI Seattle 2023

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Baseline characteristics

	Female	Male
Prevalence of MAFLD	17.7%	24.3%
Prevalence of liver fibrosis	10.7%	13.4%
Black ethnicity	48%	17%
ALT, U/L	26.4 ± 20.4	33.4 ± 22.5
HDL cholesterol, mmol/l	1.46 ± 0.57	1.11 ± 0.33
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  - 7.0 vs. 5.9 per 100 PY

particularly **after 50 years old**

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On multivariable cox regression and after age adjustment: **MAFLD** (aHR 3.3, 95% CI 2.0-5.6) **and female sex** (aHR 2.2, 95% CI 1.3-3.5) **were independent predictors** of developing significant liver fibrosis while **CD4 cell count was protective** (aHR 0.99, 95% CI 0.99-0.99).

Kablawi et al. CROI Seattle 2023

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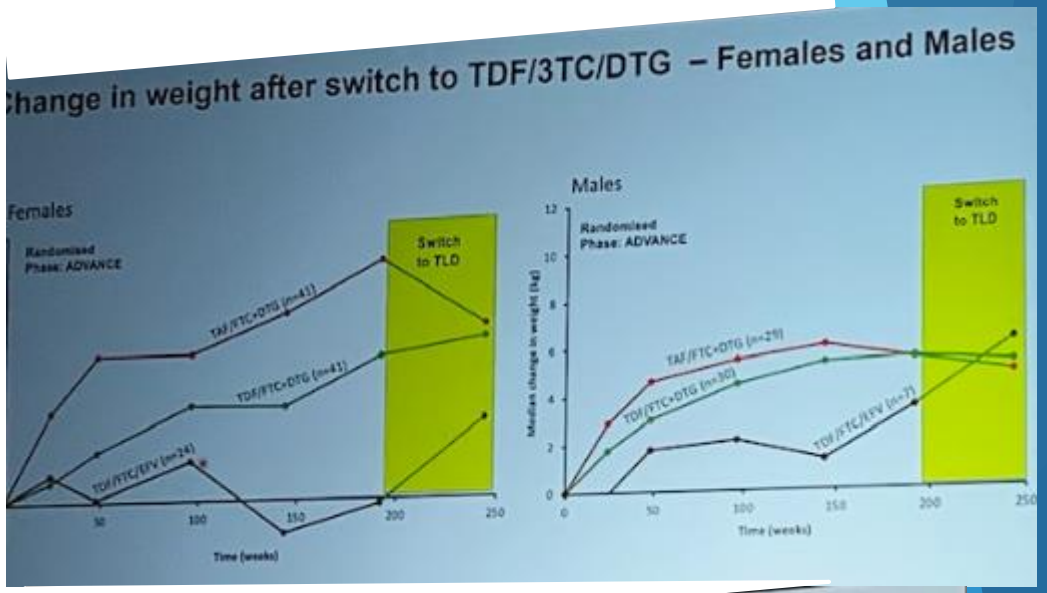
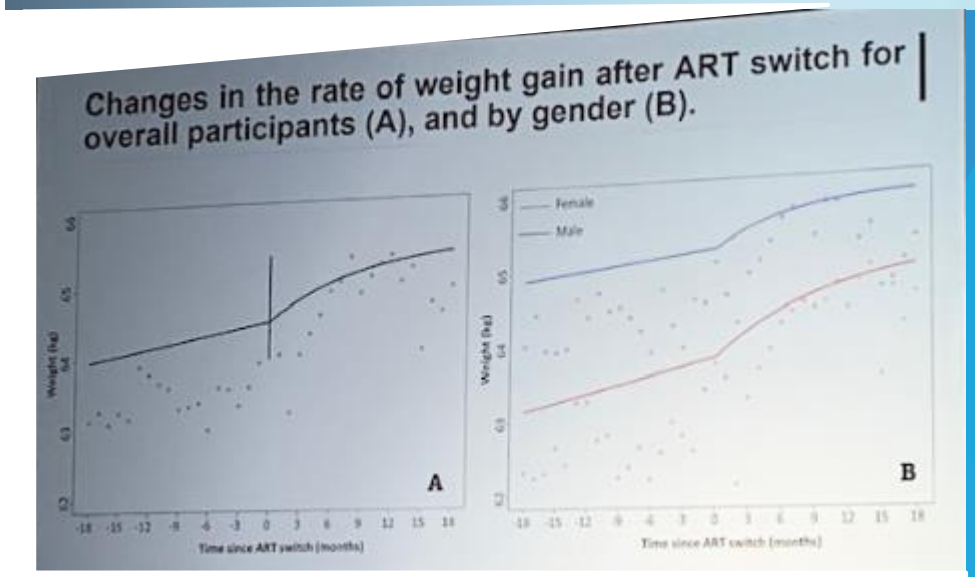
- MAFLD seems to be a sexual dimorphic disease in PWH
- Despite having lower rates of MAFLD, women with HIV have higher incidence of significant liver fibrosis compared to men
  - Especially after 50 years of age
- Future studies should target adequate consideration of sex differences in clinical investigation of MAFLD to fill current gaps and implement precision medicine for PWH
  - Hormone data, drug exposure, viral co-infection

Weight loss and metabolic changes after switching from TAF/FTC/DTG to TDF/3TC/DTG

- ADVANCE study
- At 192w most switched to TLD
- Reviewed these pts at 52w
- Significant reduction in TC, LDL and TG, fasting glucose and HBa1c on switching from TAF to TDF, and HBa1c EFV to DTG
- Women lost median 1.6kg TDF to TAF switch
- EFV to DTG switch saw 2.9kg wt gain





Bosch, et al. CROI.Seattle 2023

INSTI and weight gain in women

Introduction and Background

JOHNS HOPKINS MEDICINE

Antiretroviral therapy (ART), especially treatments containing integrase strand transfer inhibitors (INSTIs), has been associated with weight gain in both ART-initiation and switch studies, especially in women, and yet the underlying mechanisms are unclear.

	White	Brown	Beige/Brite
Lipid storage and mobilization	+++	++	++
Mitochondria	+	+++	++
Respiratory Chain	+	+++	++
Fatty Acid oxidation	+	+++	++
Uncoupling Protein 1 (UCP1)	-	+++	++

Kim, et al. CROI Seattle 2023

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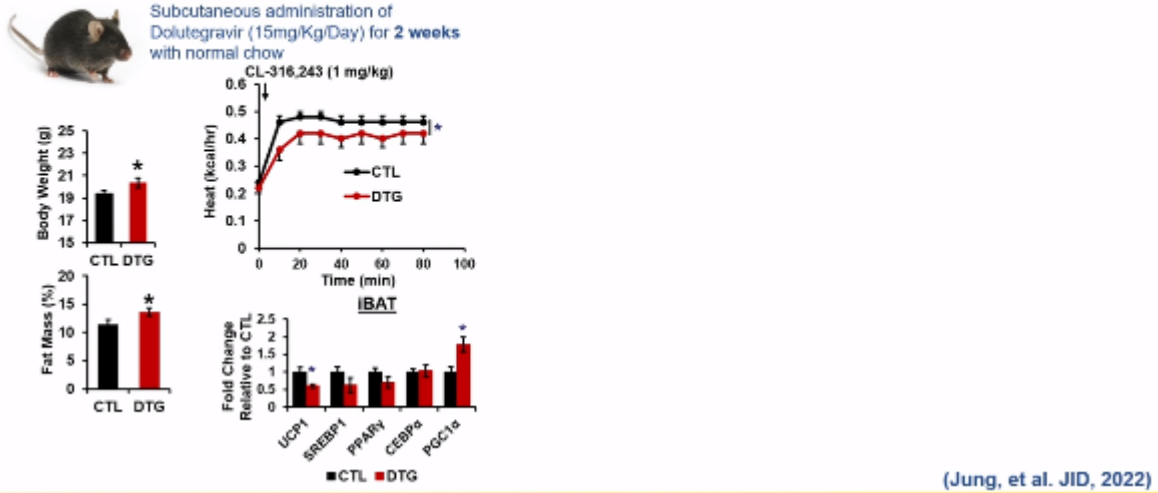
Dolutegravir Suppresses Thermogenesis in Preclinical Model (Rodent and In vitro System)

JOHNS HOPKINS MEDICINE



(Jung, et al. JID, 2022)

- 2 weeks DTG in rodent sufficient to cause weight gain
- Potent inhibitor of UCP1 and various others agents
- Suppresses thermogenesis by through disrupted mitochondrial respiration, reduced lipolysis, reduced glucose uptake & increased insulin resistance

Kim, et al. CROI Seattle 2023

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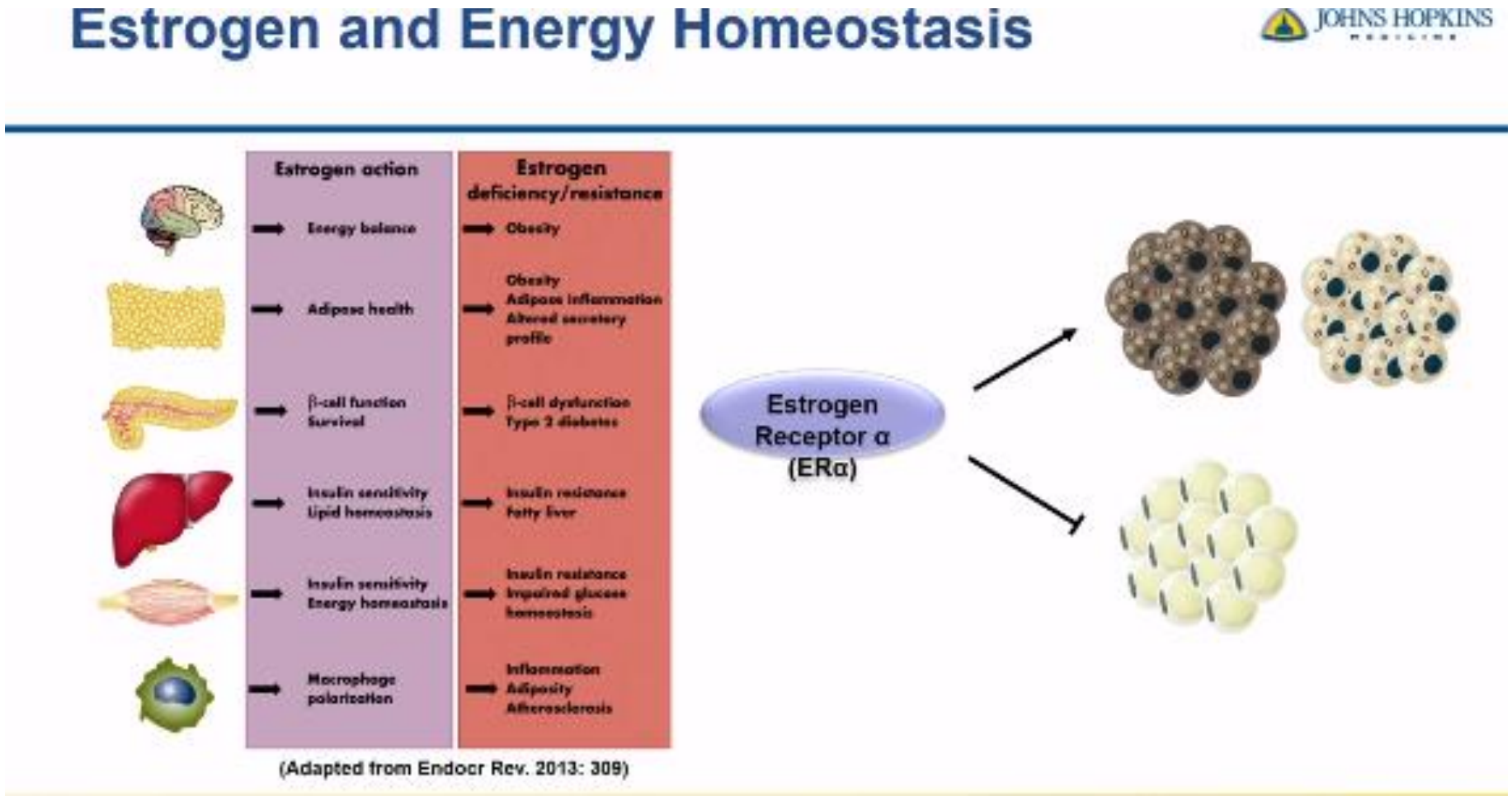
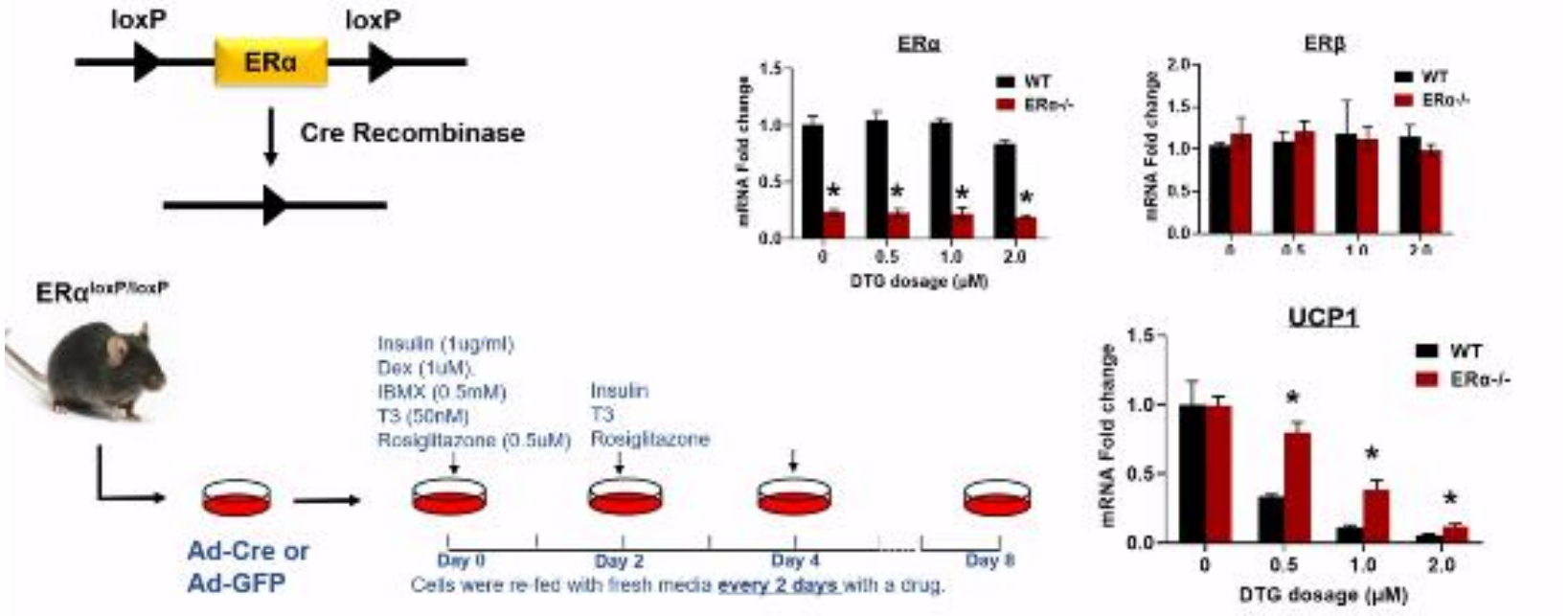


- Estrogen receptor alpha deficiency increases weight gain, glucose dysregulation and insulin resistance
- Could this be mode of action of DTG associated weight gain?

A loss of ERα Attenuates DTG-mediated suppression of UCP1 in Brown Adipocytes



- Our data showed that DTG inhibits estrogen signaling action modulated by ERa and a genetic deletion of ERa in adipocytes attenuates DTG-mediated suppression of thermogenesis
- These findings suggest a novel mechanism by which INSTIs may lead to weight gain potentially in a sex-dependent manner

Paediatric cure 1, Philip J Goulder, Oxford

- Early life immunity v adult immunity
  - Superior outcomes compared to adults covid vzv HIV cure
  - Untreated HIV VL in infants exceeds 1000000 c/ml throughout first few years of life, then decreases after age 5yo vs adult set point 4-6 weeks
  - Mortality untreated children 40% in first 2 years
  - HLAB types in children don't affect VL eg HLAB18
  - Viremic non progressors common 5-10% children vs 29 cases ever in adults
  - bnAB response in children more potent and greater breadth than adults - >75% in children vs 20% in adults, all untreated
  - Therefore is there higher potential for cure?
    - Early life immunity
    - Early start of ART
    - Mothers can have protective or susceptible alleles which they pass onto children

      VISCONTI cohort – cART 1-3m post infection

      KN cohort all in utero acquisition, treated AZT NVP or NVP started between 1d (POCT) and 12d(std test). NO VL difference at 1m: NK responses even in utero can keep VL reservoir lower therefore making cure more possible – HLA mediated. Similar to Visconti

Paediatric cure 2

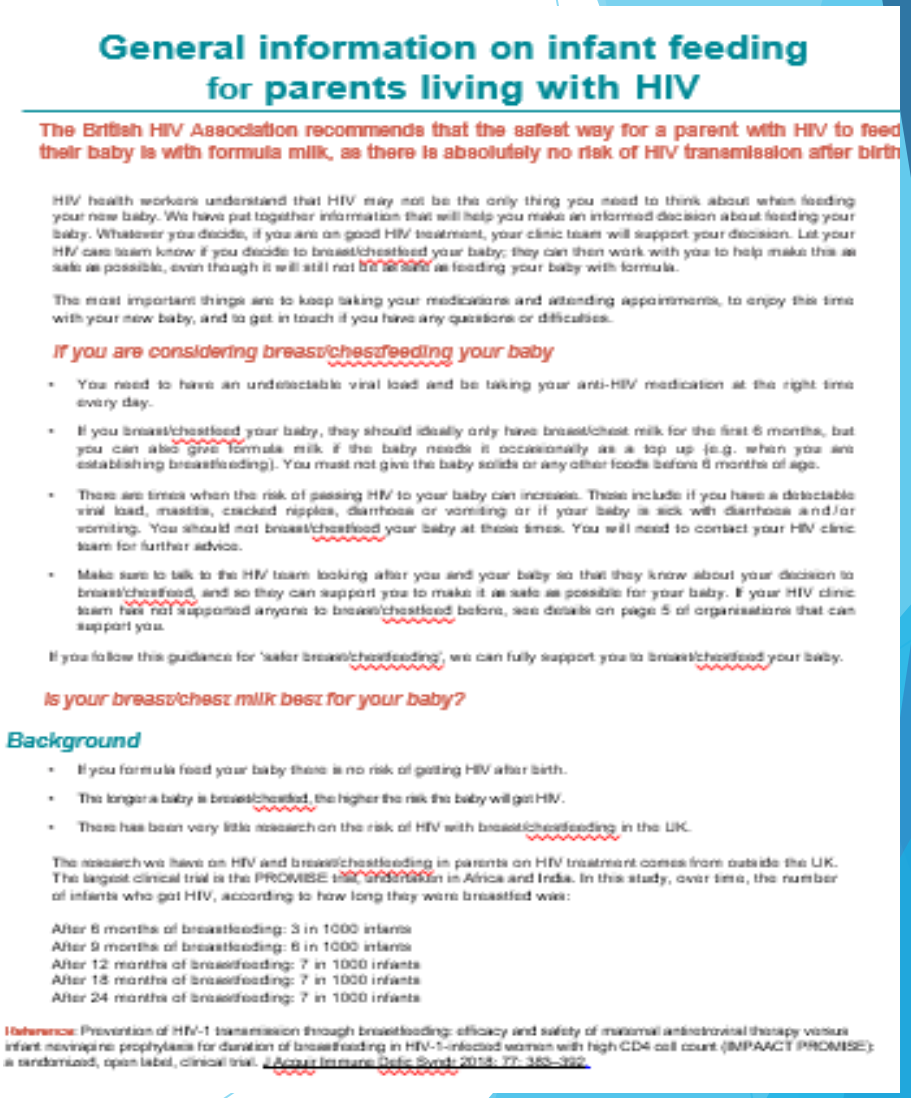
- Viral differences child vs adult
- cART reduces transmission and impacts paediatric reservoir – cART starts working very early, even before birth: mothers usually on treatment at delivery, children have v low VL at birth, 1:7 children aviremic at birth: therefore cure more possible
- Adult and CWH RNA and DNA during treatment are different
- Adult DNA suppresses a log but not UD, CWH suppresses to UD within 6m and stays there. Suggests reservoir lower
- Replicative capacity of transmitted virus is lower in VT not horizontal transmission
- Gender differences: virus transmitted to females are IFN resistant. Females rebound more quickly than males with same non adherence

Cure options

- Very early cART
- T cell vaccine
- bNABs: passive or genetically induced
- Analytical treatment interruption to maxmise vaccinal effects and reverse latency (as per adult RIO study)

US Infant Feeding Guidelines, CROI and Women's Workshop

- Women can be supported to breastfeed if VL <40c/ml
- Infant PEP however has not been agreed upon
  - AZT mono?
  - Triple therapy?
  - 14 days vs 28 days vs 6 months
- 24/7 telephone helpline for advice
- Very US centric
- No UK, European or LMIC data presented
- BHIVA Infant Feeding statement 2010, 2022



General information on infant feeding for parents living with HIV

The British HIV Association recommends that the safest way for a parent with HIV to feed their baby is with formula milk, as there is absolutely no risk of HIV transmission after birth

HIV health workers understand that HIV may not be the only thing you need to think about when feeding your new baby. We have put together information that will help you make an informed decision about feeding your baby. Whatever you decide, if you are on good HIV treatment, your clinic team will support your decision. Let your HIV care team know if you decide to breast/chestfeed your baby; they can then work with you to help make this as safe as possible, even though it will still not be as safe as feeding your baby with formula.

The most important things are to keep taking your medications and attending appointments, to enjoy this time with your new baby, and to get in touch if you have any questions or difficulties.

If you are considering breast/chestfeeding your baby

- You need to have an undetectable viral load and be taking your anti-HIV medication at the right time every day.
- If you breast/chestfeed your baby, they should ideally only have breast/chest milk for the first 6 months, but you can also give formula milk if the baby needs it occasionally as a top up (e.g. when you are establishing breastfeeding). You must not give the baby solids or any other foods before 6 months of age.
- There are times when the risk of passing HIV to your baby can increase. These include if you have a detectable viral load, mastitis, cracked nipples, diarrhoea or vomiting or if your baby is sick with diarrhoea and/or vomiting. You should not breast/chestfeed your baby at these times. You will need to contact your HIV clinic team for further advice.
- Make sure to talk to the HIV team looking after you and your baby so that they know about your decision to breast/chestfeed, and so they can support you to make it as safe as possible for your baby. If your HIV clinic team has not supported anyone to breast/chestfeed before, see details on page 5 of organisations that can support you.

If you follow this guidance for 'safer breast/chestfeeding', we can fully support you to breast/chestfeed your baby.

Is your breast/chest milk best for your baby?

Background

- If you formula feed your baby there is no risk of getting HIV after birth.
- The longer a baby is breast/chestfed, the higher the risk the baby will get HIV.
- There has been very little research on the risk of HIV with breast/chestfeeding in the UK.

The research we have on HIV and breast/chestfeeding in parents on HIV treatment comes from outside the UK. The largest clinical trial is the PROMISE trial, undertaken in Africa and India. In this study, over time, the number of infants who got HIV, according to how long they were breastfed was:

After 6 months of breastfeeding: 3 in 1000 infants
After 9 months of breastfeeding: 6 in 1000 infants
After 12 months of breastfeeding: 7 in 1000 infants
After 18 months of breastfeeding: 7 in 1000 infants
After 24 months of breastfeeding: 7 in 1000 infants

Reference: Prevention of HIV-1 transmission through breastfeeding: efficacy and safety of maternal antiretroviral therapy versus infant nevirapine prophylaxis for duration of breastfeeding in HIV-1-infected women with high CD4 cell count (IMPAACT P1078): a randomised, open label, clinical trial. J Acquir Immune Defic Syndr 2018; 77: 383–392

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Thank you