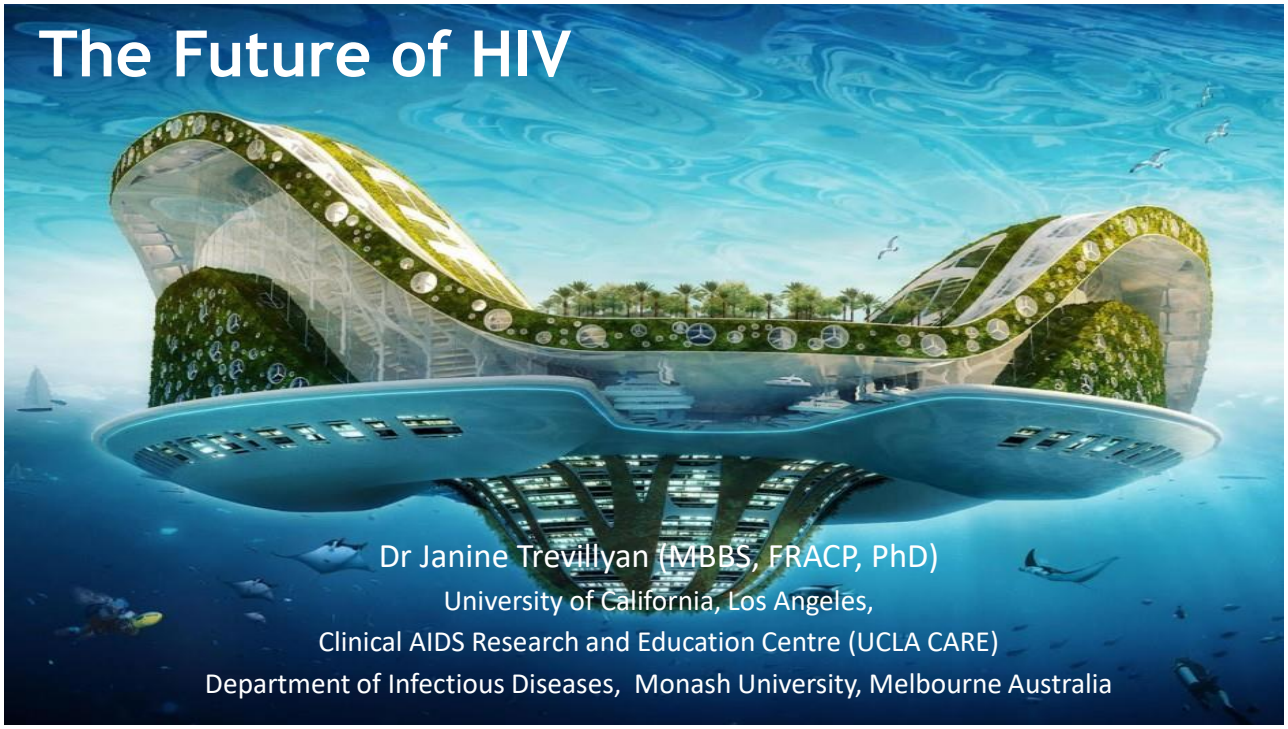

Dr Janine Trevillyan (MBBS, FRACP, PhD)
University of California, Los Angeles,
Clinical AIDS Research and Education Centre (UCLA CARE)
Department of Infectious Diseases, Monash University, Melbourne Australia

Conflicts of Interest

- I have received honoraria from Gilead Health Sciences for speaker responsibilities unrelated to this talk

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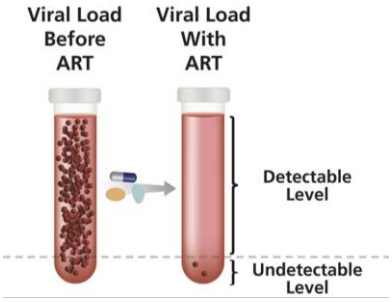
Where are we now: May 2019

Highly effective drugs

Modest side effect profiles



Viral suppression achievable in most

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Cure efforts and prevention strategies are ramping up

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What's the future for those living with well controlled HIV?

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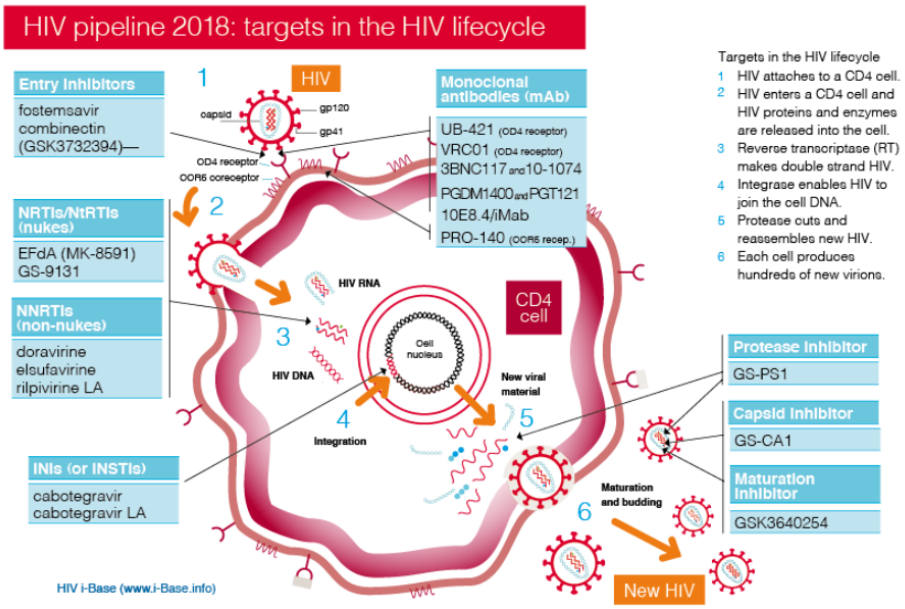

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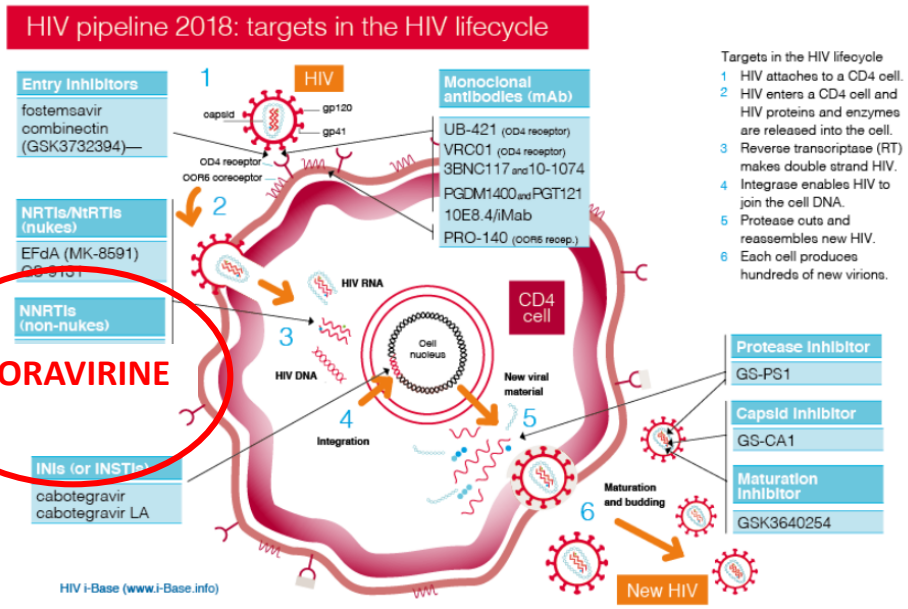

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Doravarine

- Novel, next generation NNRTI
- Unique resistance profile with invitro activity against most prevalent NNRTI resistance mutations
  (RT K103N, Y181C, G190A, K103N, Y181C & E138K)
- Low potential for drug-drug interactions
- Dosed once daily with or without food
- Being developed as a single entity and as a fixed dose combination with Emtricitabine and Tenofovir Disoproxil Fumerate (by Merck: Delstrigo™)

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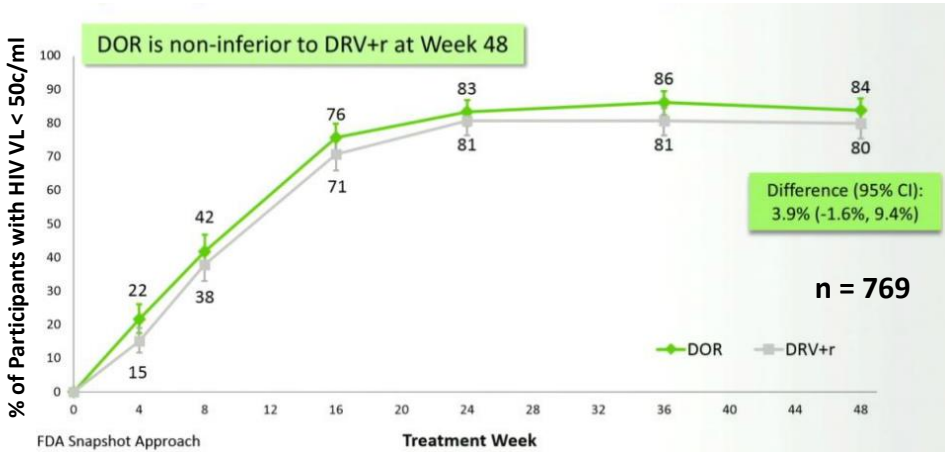
DRIVE-FORWARD

- Naïve
- No-baseline resistance
- DOR vs DRV/r with 2NRTI



Molina et al. *Lancet ID* 2018;5(5):e211

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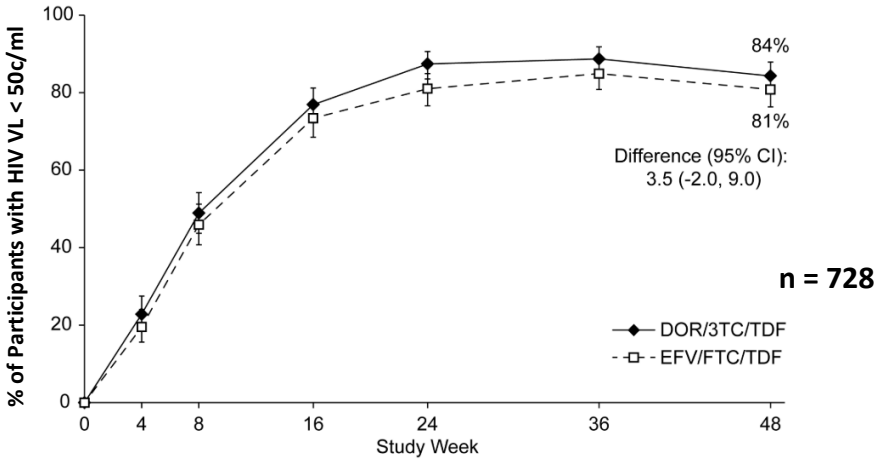
DRIVE-AHEAD

- Naïve
- No-baseline resistance
- DOR vs EFV with TDF/3TC



Orkin et al. *CID* 2019;68(4):535

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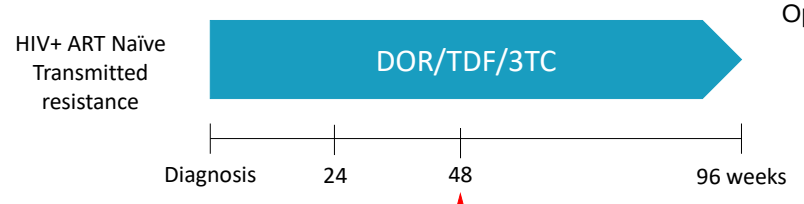
Where will doravarine be used?

- DRIVE 2Simplify (DOR/3TC and new NRTI)
- DRIVE-BEYOND: DOR in treatment experienced with transmitted resistance

Open label, multicentre, single arm



Genotype with **one** of the following:
- K103N
- Y181C
- G190A

Primary endpoint
HIV-1 RNA < 50c/ml

Secondary endpoints:
- Adverse events and discontinuations due to AEs

ClinicalTrials.gov: NCT02629822

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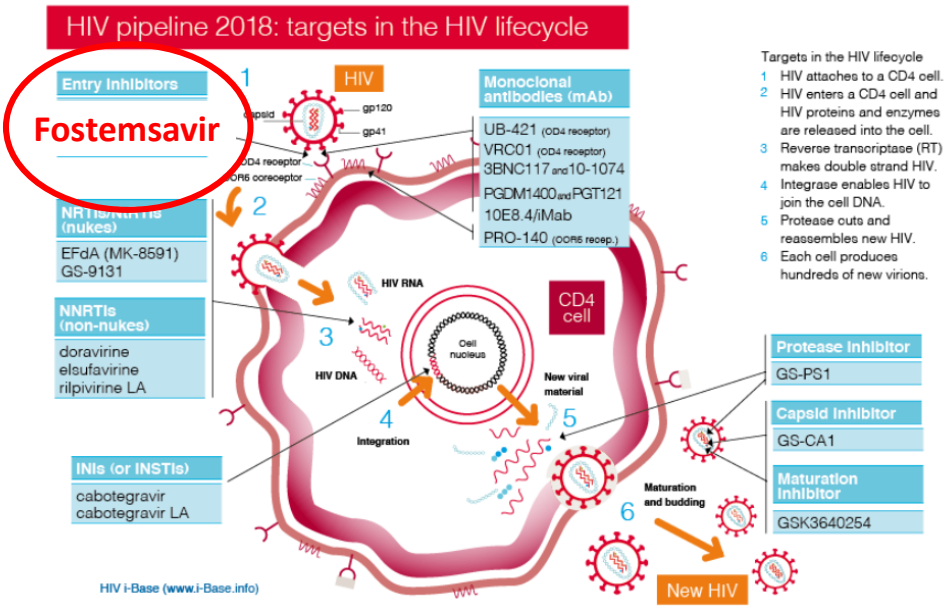

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Fostemsavir (GSK3684934)

- gp120 attachment inhibitor
- Pro-drug metabolised to it's active metabolite: Temsavir
- Binds to viral envelope glycoprotein (gp120) preventing the virus from binding to CD4+ T cells
- First drug in a new class so anticipated roll in those with drug resistance
- In-vitro no cross resistance to any other antiretroviral classes

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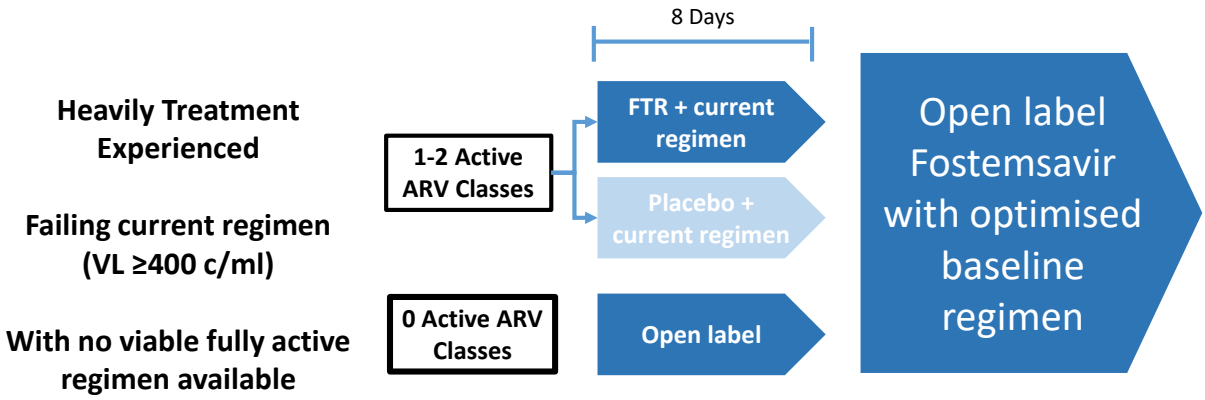
BRIGHTE Study



Aberg et al. 2018 HIV Drug Therapy Glasgow; Abstract 0334A

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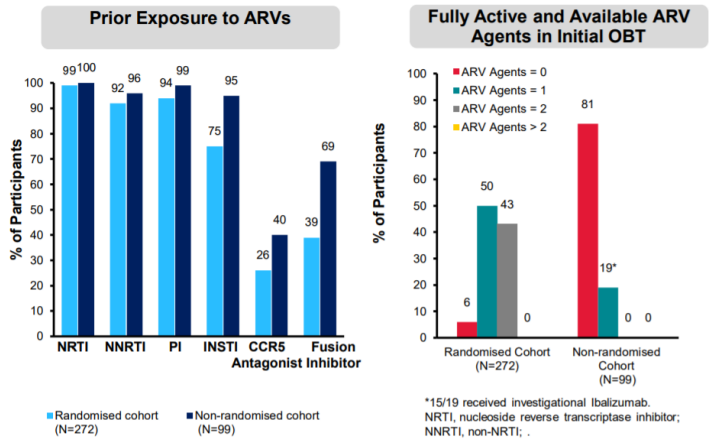
BRIGHTE Study: Participants heavily treatment experienced with no or few fully active ARV agents available



Aberg et al. 2018 HIV Drug Therapy Glasgow; Abstract 0334A

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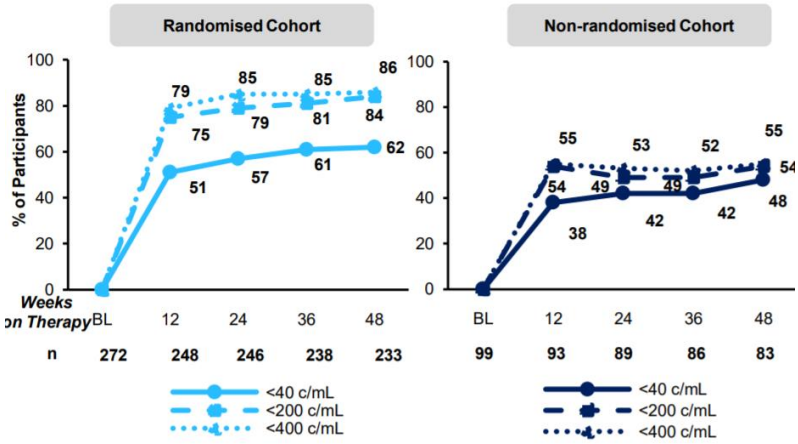
Fostemsavir led to HIV suppression in a significant proportion of participants



Aberg et al. 2018 HIV Drug Therapy Glasgow; Abstract 0334A

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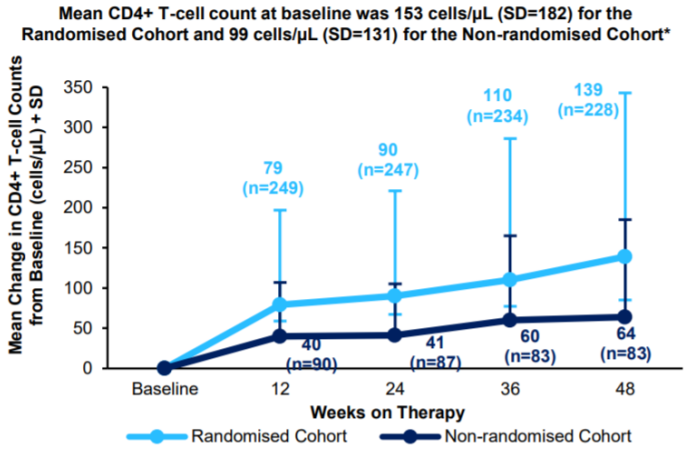
Modest but significant improvements in CD4+ T cell count even in those heavily immunocompromised at baseline



Aberg et al. 2018 HIV Drug Therapy Glasgow; Abstract 0334A

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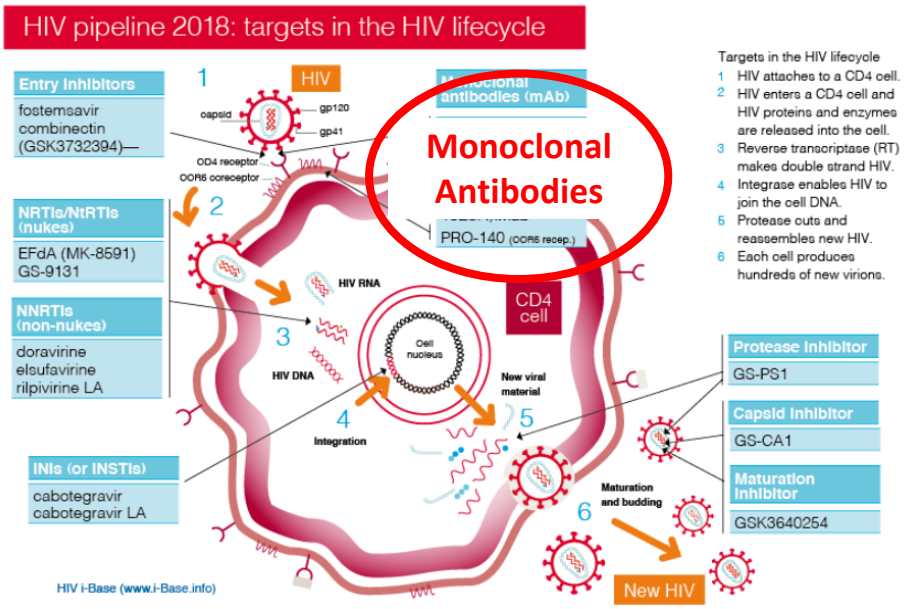

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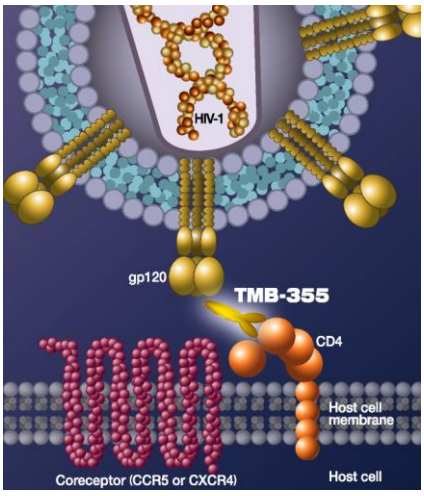
Ibalizumab (Trogarzo)

- gp120 Attachment inhibitor
- Initial loading dose and then IV infusion every 2 weeks
- Needs to be used in combination with other ART
- Approved by FDA for people with triple class resistance
- Price in the US is $US 118,000



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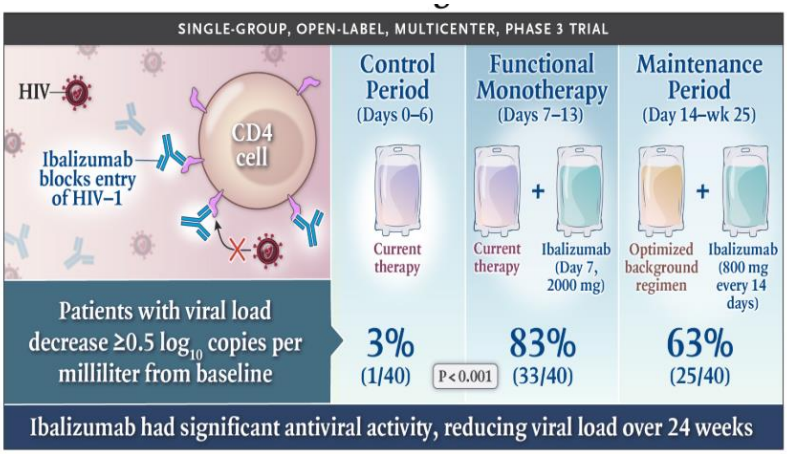
Ibalizumab for treatment experienced HIV

n=40

Heavily Treatment Experienced

Failing current regimen (VL ≥400 c/ml)

With no viable fully active regimen available



Emu et al. NEJM 2018;379:645

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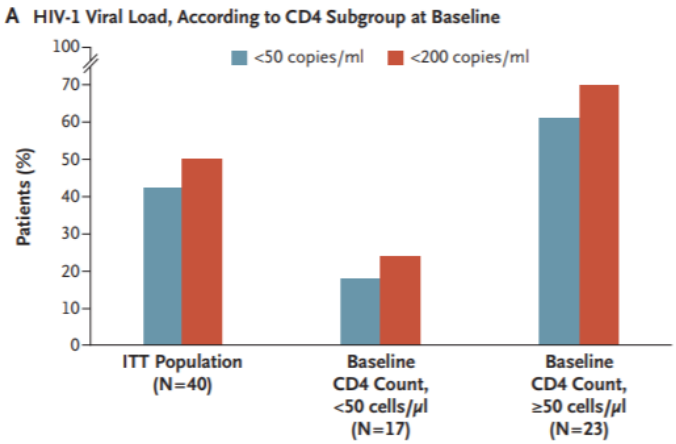
Ibalizumab for treatment experienced HIV



Emu et al. NEJM 2018;379:645

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Table 3. Adverse Events in the 40 Study Patients.

Adverse Event	No. of Patients (%)
Any adverse event*	32 (80)
Assessed as related to ibalizumab†	7 (18)
Leading to discontinuation of ibalizumab	5 (13)
Occurring in patients who died	4 (10)
Serious adverse event‡	9 (23)
Adverse event reported in >5% of patients	
Diarrhea	8 (20)
Dizziness	5 (13)
Fatigue	5 (13)
Nausea	5 (13)
Pyrexia	5 (13)
Rash§	5 (13)
Vomiting	4 (10)
Lymphadenopathy	4 (10)
Nasopharyngitis	4 (10)
Decreased appetite	3 (8)
Excoriation	3 (8)
Headache	3 (8)
Upper respiratory tract infection	3 (8)

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Adverse Effects

- Diarrhoea the most common
- 1x serious immune reconstitution illness deemed secondary to ibalizumab
- Most serious adverse events secondary to underlying advanced HIV

Emu et al. NEJM 2018;379:645

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HIV drug pipeline is alive and well, but……

New drugs are expensive, not yet here, and there may be unpredicted side effects that limit use

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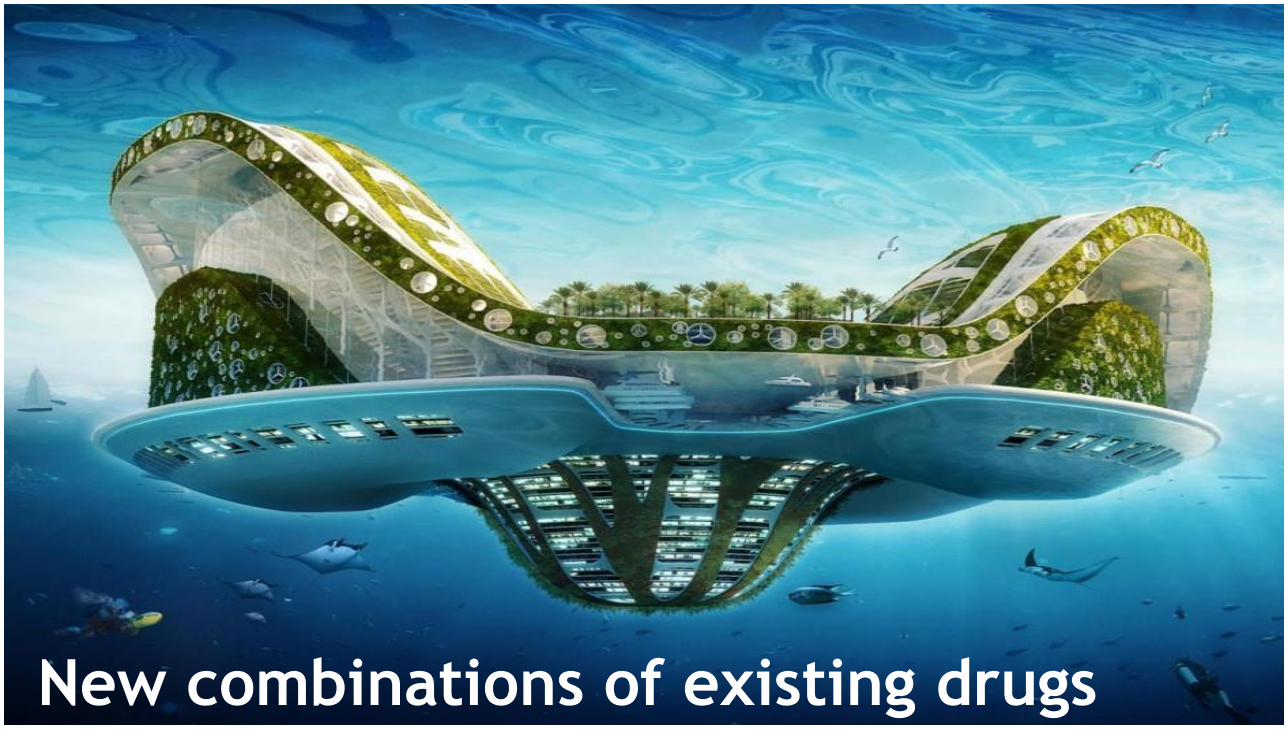

Why all the Interest in dual therapy regimens?

- **Minimise toxicity**
  - No tenofovir or abacavir needed
  - Low propensity for drug interactions
- Small pill burden= **high patient satisfaction**
- **Cost $$**
  - Predicted to cost US $36/patient/year
  - Mathematical modelling suggests that if DTG/3TC as effective as cART the USA would save >$500 million in ART costs over 5 years

Girouard CID 2016;62(6):784-91

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ARV monotherapy is not the answer

- Some evidence that PI monotherapy may be ok in some cases but there is a consistent signal for reduced efficacy (10-15%).

- DOMONO
  - Randomized patients to immediate versus delayed switch to DTG monotherapy
  - At 24 weeks: 4/50 in monotherapy versus 0/53 cART failed
  - A further 7 failed in the second 24 weeks
  - 3 developed integrase resistance mutations
  - All who failed had adequate DTG levels

Wijting et al. Lancet HIV: 2017;4(12):PE547

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ASHM commentary on the DHHS Guidelines

Preferred 1st Line regimen (INSTI + 2 NRTI)

Dolutegravir/abacavir/lamivudine
Dolutegravir plus tenofovir/emtricitabine
Elvitegravir/cobicistat/tenofovir/ emtricitabine
Raltegravir plus tenofovir/emtricitabine

Selection of a regimen should be individualized and guided:

- Virologic efficacy
- Toxicity
- Pill burden
- Dosing frequency
- Drug-drug interaction potential
- Resistance testing results,
- Comorbid conditions
- Cost

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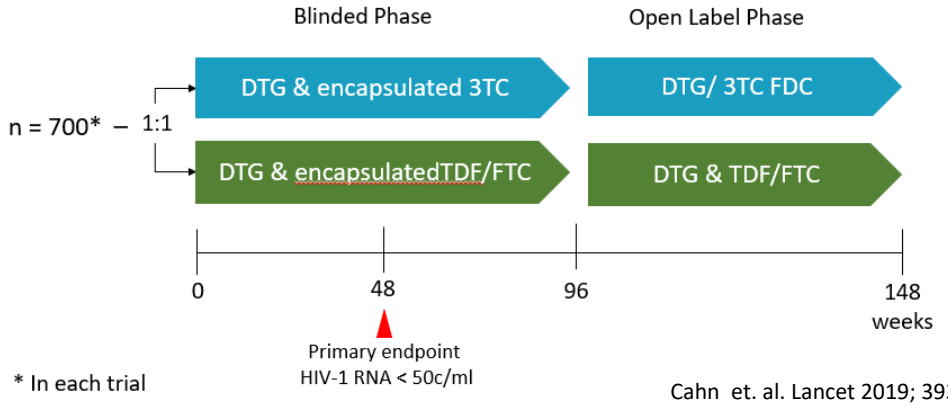
GEMINI I & II

Two identical Phase III, Randomised, Double Blind, Multicentre, Parallel Group, Non Inferiority Studies of DTG/3TC treatment regimen in naïve



Cahn et. al. Lancet 2019; 393 (10167):143

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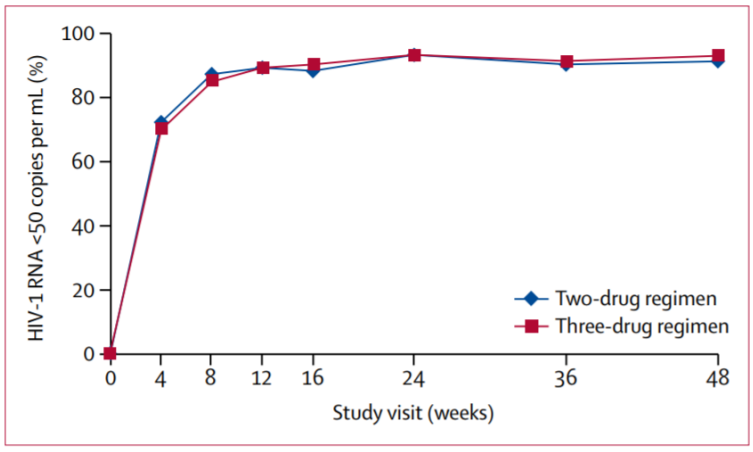
Gemini Trials: DTG/3TC versus DTG/TDF/3TC



Cahn et. al. Lancet 2019; 393 (10167):143

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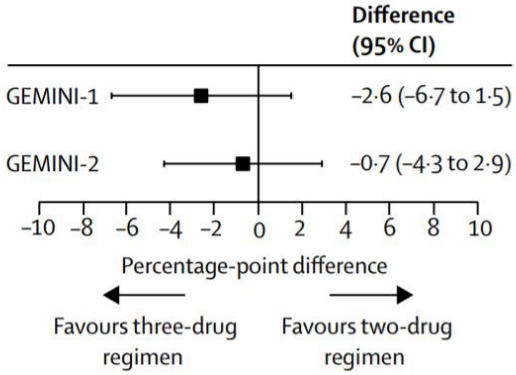
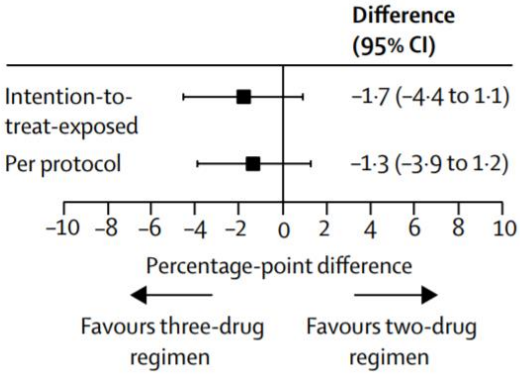
Gemini Trials: DTG/3TC versus DTG/TDF/3TC





Cahn et. al. Lancet 2019; 393 (10167):143

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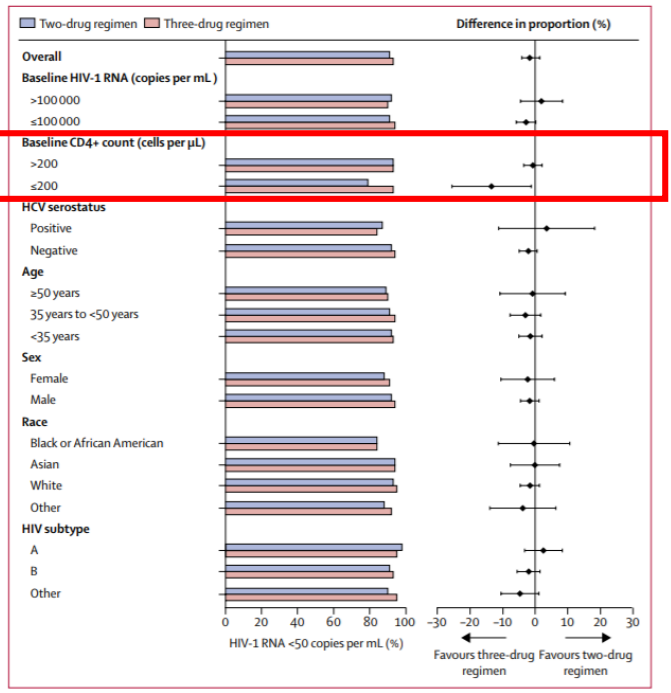

Gemini Trials Subgroup analysis

Some signals of when to be cautious

Cahn et. al. Lancet 2019; 393 (10167):143

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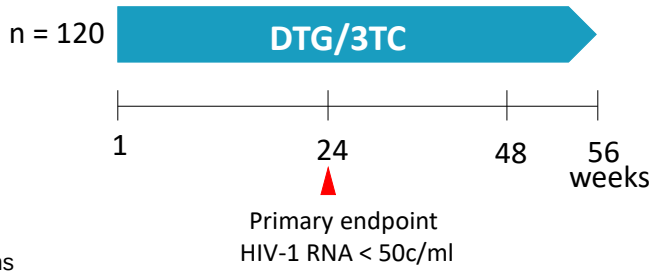
ACTG 5353: Dolutegravir Plus Lamivudine Dual Therapy in Treatment Naïve HIV-1 Patients

Phase II, single-arm, open-label, pilot study of DTG/3TC

Inclusion
- HIV +ve
- Adults
- ART Naïve
- HIV VL>1,000 c/ml
- HIV VL<500,000 c/ml

Exclusion
- Mod-severe hepatic impairment
- Hepatitis B infection
- Active drug or alcohol use
- Presence of resistance mutations



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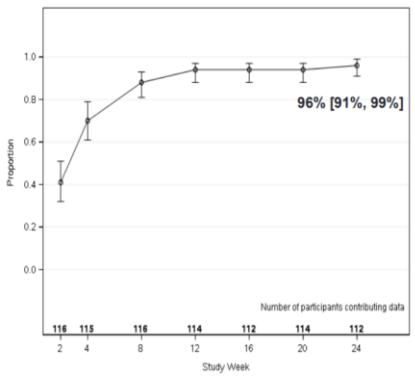
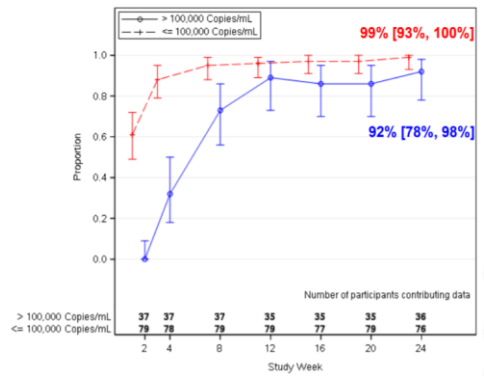
As-treated analysis; proportion of participants with HIV-1 RNA < 50 copies/mL by week 24

Overall



Stratified by baseline VL



HIV VL at Baseline
>100,000
≤100,000

Taiwo, B et. al. IAS 2017, Paris Abstract No: MOAB0107LB

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Previous studies of two-drug ART have raised warning flags about resistance and failure rates

Trial	n	Design	Outcome
ACTG 5142	757	LPV/r + 2NRTIs vs EFV + 2NRTs vs LPV/r + EFV	LPV/r + EFV associated with NNRTI resistance and lipid abnormalities
PROGRESS	206	LPV/r + RAL vs LPV/r + TDF/FTC	LPV/r + RAL was non-inferior but mean baseline HIV-1 RNA was low (~18,000 copies/mL)
ACTG 5262	112	DRV/r + RAL single arm	Increased virologic failure if baseline HIV-1 RNA > 100,000 copies/mL
SPARTAN	94	ATV + RAL BID vs ATV/r +TDF/FTC	ATV + RAL was associated with increased virologic failure and jaundice
RADAR	85	DRV/r + RAL vs DRV/r + TDF/FTC	More failure with DRV/r + RAL
NEAT	805	DRV/r + RAL vs DRV/r + TDF/FTC	Non-inferior overall; Higher virologic failure when baseline HIV-1 RNA was >100,000 copies/mL or CD4+ < 200 cells/mm^3.
GARDEL	217	LPV/r + 3TC vs LPV/r + 2NRTIs	LPV/r + 3TC non-inferior regardless of baseline HIV-1 RNA
MODERN	797	MVC + TDF/FTC vs MVC + DRV/r	MVC + DRV/r inferior

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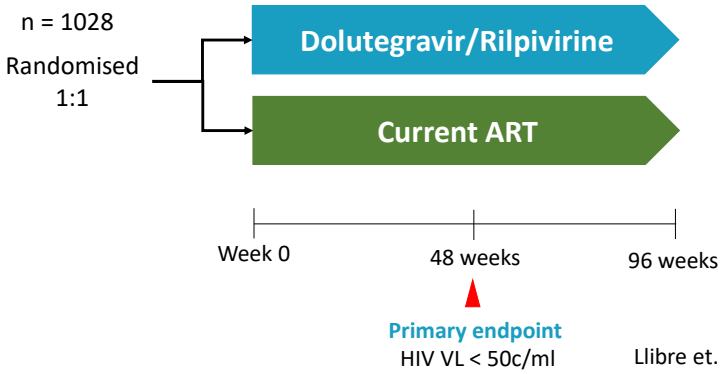
Dolutegravir/Rilpivirine (Juluca) Sword 1 & 2

Open-label, parallel-group, multicentre, phase 3, randomised, non-inferiority studies in 12 countries in suppressed individuals



- Needs to be taken with food
- Number of drug interactions

Llibre et. al. Lancet 2018; 391 (10123):839

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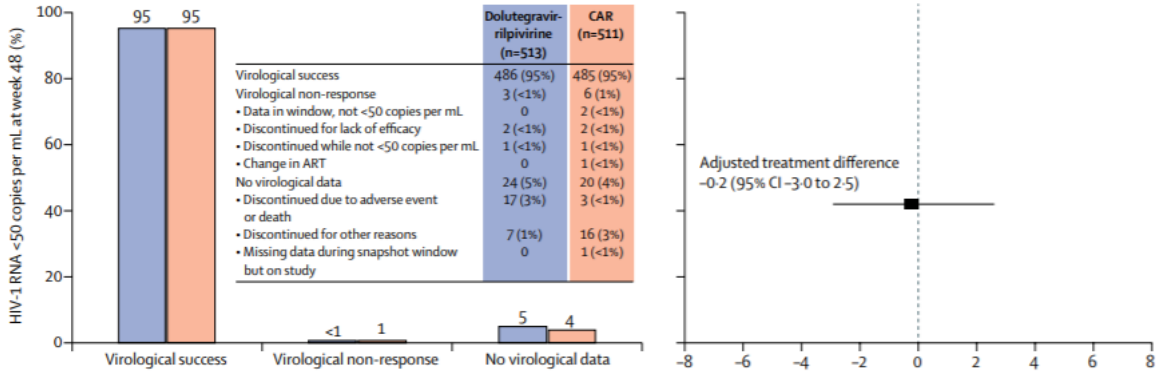
Sword 1 & 2 Intention to treat Results



Llibre et. al. Lancet 2018; 391 (10123):839

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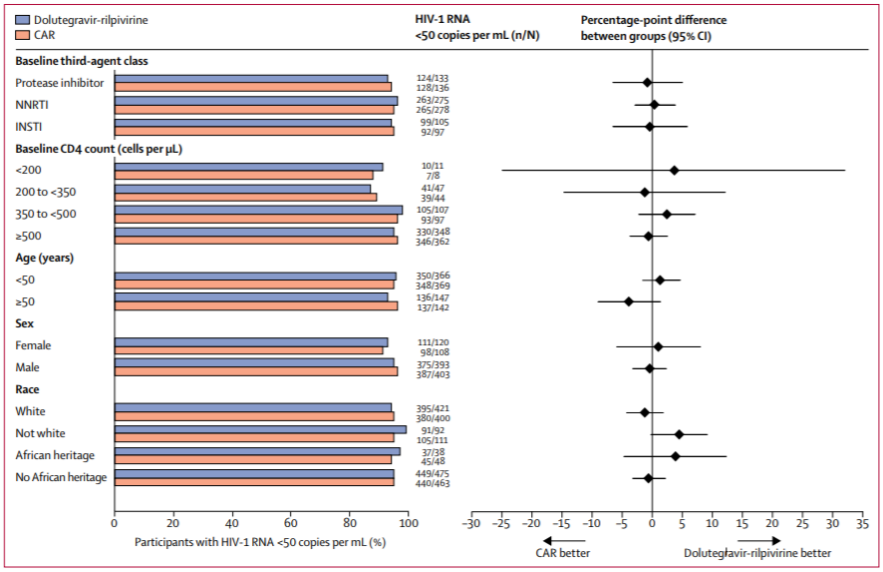
Sword 1 & 2 Intention to treat Results



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What we don't yet know about dual therapies

- Are they enough to control viral reservoir
- Is there going to be a side effect benefit when compared with three-drug TAF regimens
- ? Associated with higher levels of immune activation
- ? Applicability in special populations
  - Breast feeding women
  - Effectiveness when prior resistance or high viral loads
  - African and Asian settings
  - Advanced HIV at presentation

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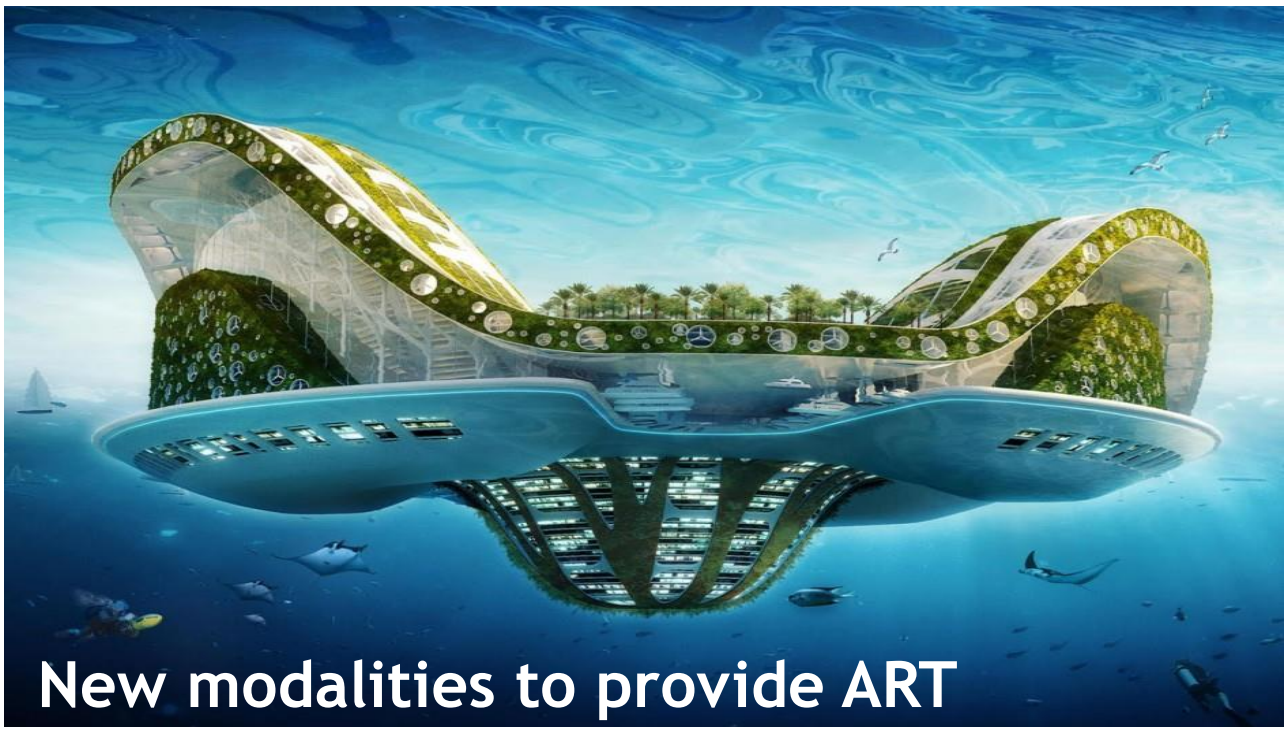

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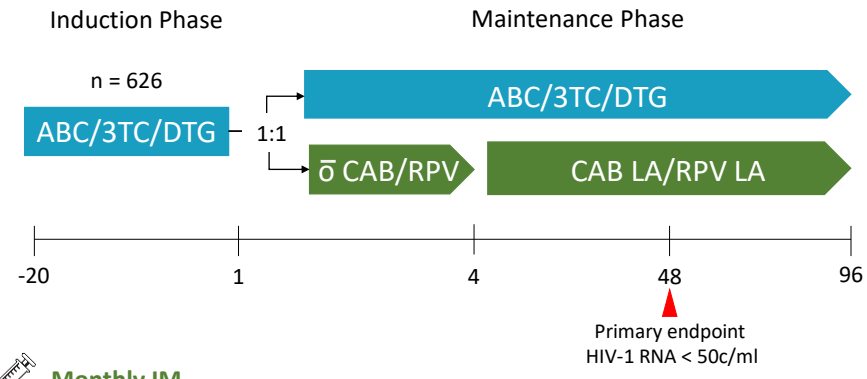
FLAIR (First Long-Acting Injectable Regimen)

Phase III, randomised, open-label, multicentre, parallel-group, non-inferiority study

ARV Naïve Individuals with no NNRTI resistance mutations



Cabotegravir:
Integrase Inhibitor

Rilpivirine:
NNRTI

Monthly IM

Orkin et. al. CROI Seattle WA 2019 Abstract 140

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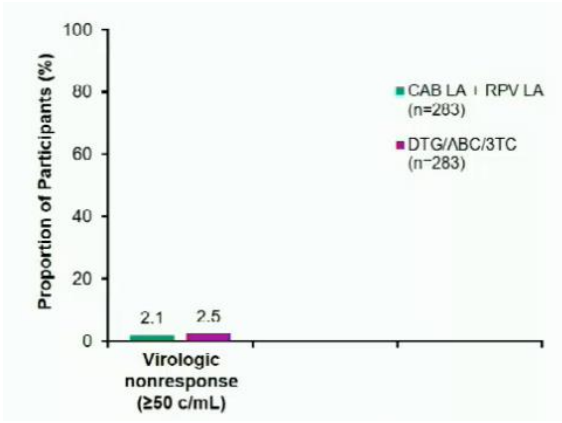
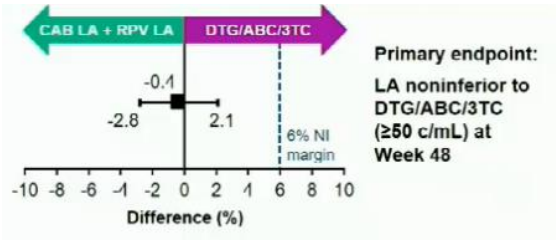
FLAIR (First Long-Acting Injectable Regimen)





Orkin et. al. CROI Seattle WA 2019 Abstract 140

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FLAIR (First Long-Acting Injectable Regimen)

	CAB LA + RPV LA N=283	DTG/ABC/3TC N=283
Any AE (≥10%), n (%)		
Any event (per participant)	246 (87)	225 (80)
Nasopharyngitis	56 (20)	48 (17)
Headache	39 (14)	21 (7)
Upper respiratory tract infection	38 (13)	28 (10)
Diarrhea	32 (11)	25 (9)
Drug-related AEs (≥3%), n (%)		
Any event (per participant)	79 (28)	28 (10)
Headache	14 (5)	4 (1)
Pyrexia	13 (5)	0
All AEs leading to withdrawal*	9 (3)	4 (1)

Orkin et. al. CROI Seattle WA 2019 Abstract 140

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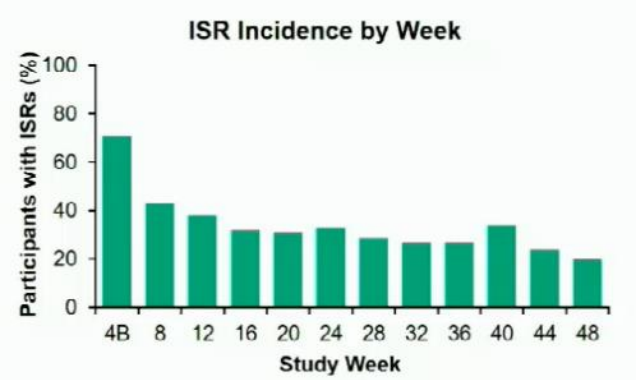
FLAIR: Participant reported injection site reactions



- The majority (99%, 2189/2203) of ISRs were grade 1–2 and most (88%) resolved within ≤7 days

Orkin et. al. CROI Seattle WA 2019 Abstract 140

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With equal exceptionally high efficacy reliably expected from all these combinations in most instances toxicity and drug interactions will be the driver

- Remember not looking for a zero side effect regimen because that doesn't exist.
- Looking to chose the regimen whose side effects and advantages match with the person in front of you

Individualised choice which will change over a lifetime

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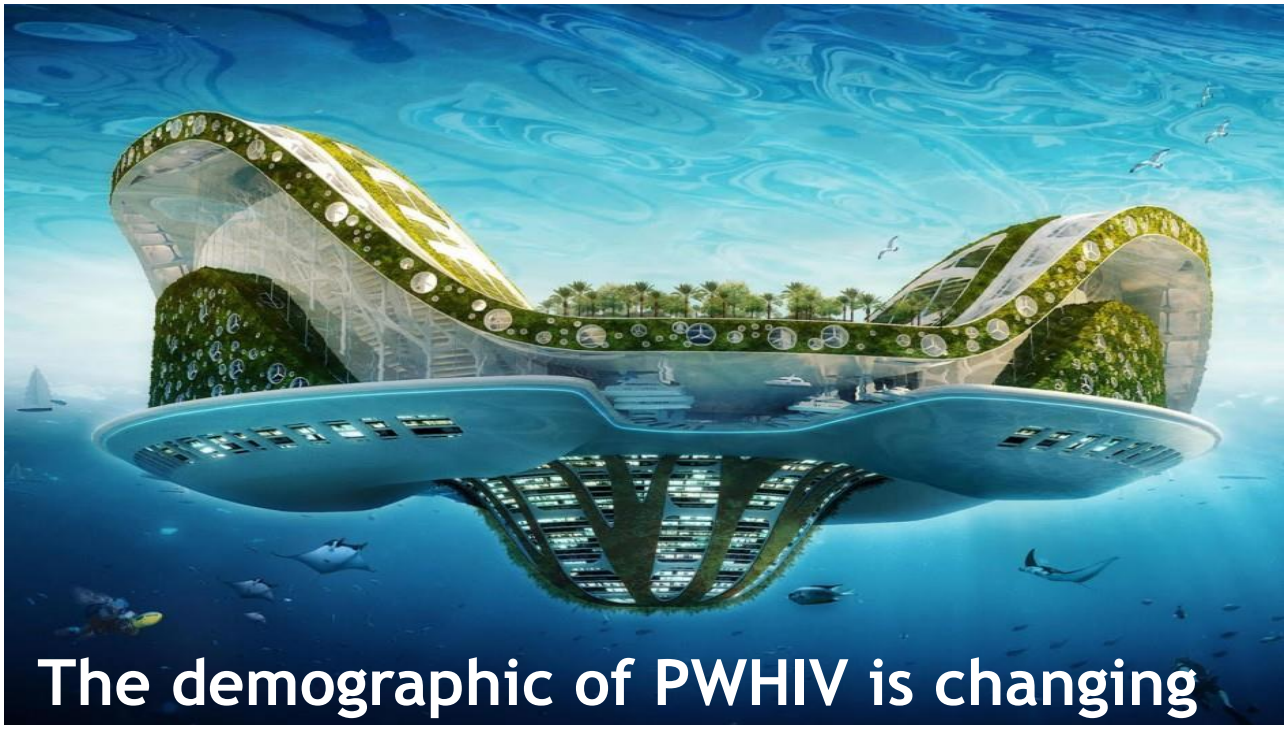
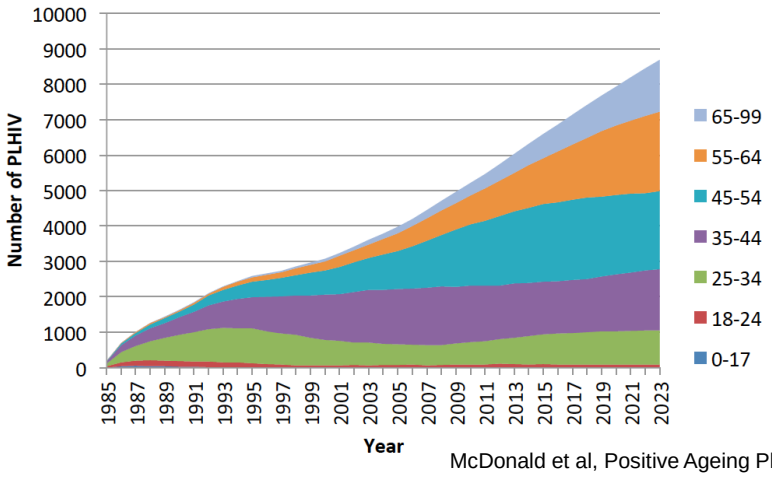


People living with HIV are ageing



McDonald et al, Positive Ageing Phase I Report 2013

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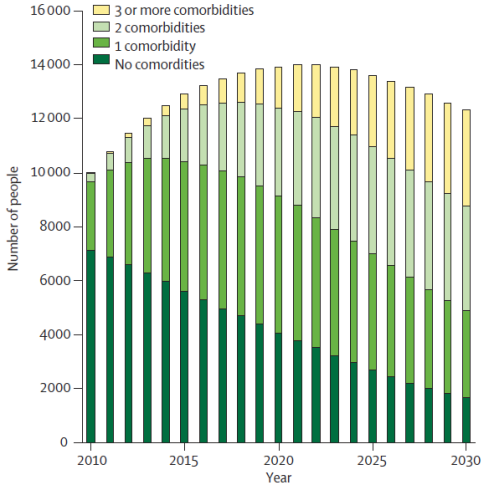
"Multi-morbidity" will be increasingly common



Smit et al. *Lancet ID* 2015; 15:810-18

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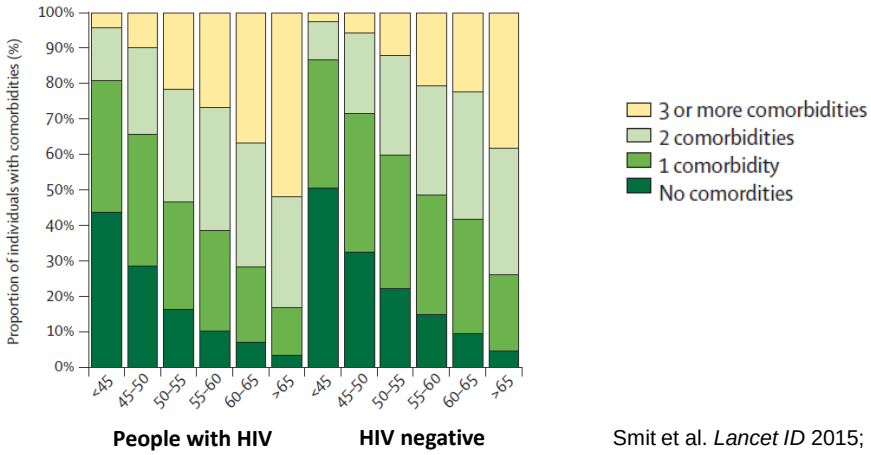
Burden of medical co-morbidity is much greater in people with HIV



Smit et al. *Lancet ID* 2015; 15:810-18

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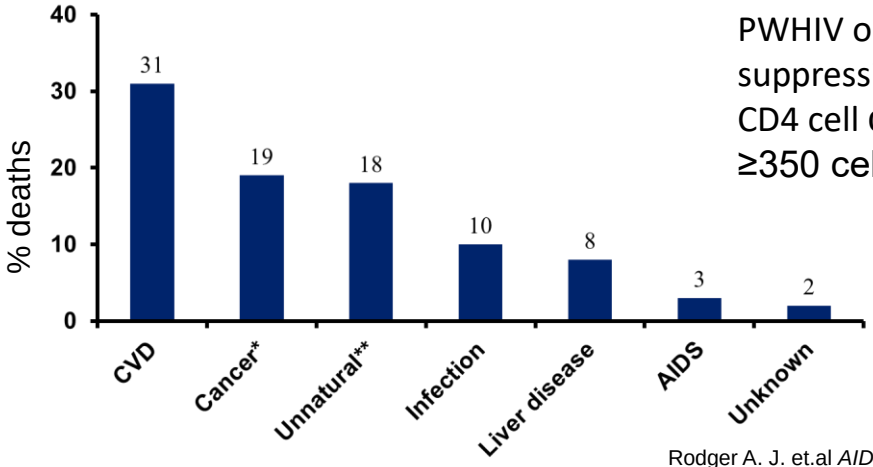
Serious non-AIDS diseases are now the leading cause of death



PWHIV on suppressive ART with CD4 cell counts ≥350 cells/mm^3

Rodger A. J. et.al *AIDS* 2013; 27(6): 973

* = non-AIDS malignancy
** = accident, suicide or violent death

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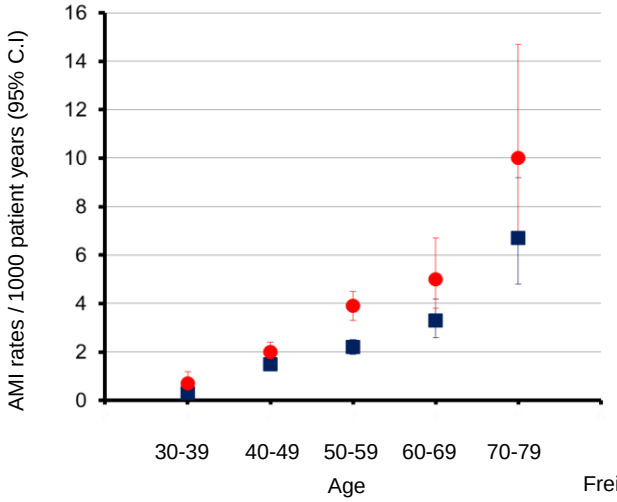
Heart Attacks are more common with HIV



* Within age group P<0.05

NA-ACCORD

Freiberg et al. *JAMA Int Med.* 2013;173(8):614

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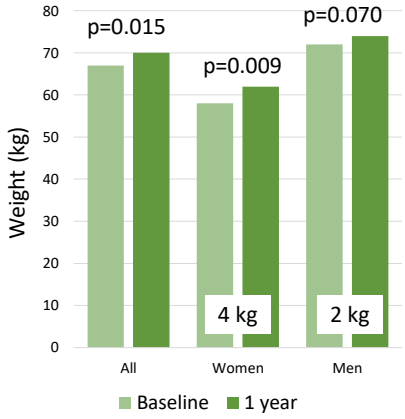
Signals that integrase inhibitors may lead to weight gain

- Retrospective analysis in France
- Triggered by 7% of patients stating weight gain as reason for DTG switch
- Switching (92%) or starting ART with dolutegravir based regimen
- Middle aged, well controlled individuals
- 59% normal BMI at baseline

20% of patients had >10% weight increase



Menard et.al. 2017 AIDS

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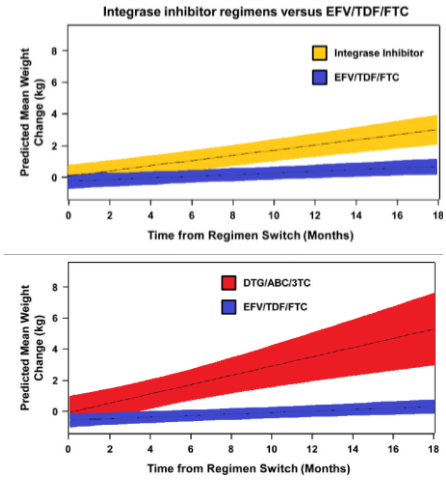
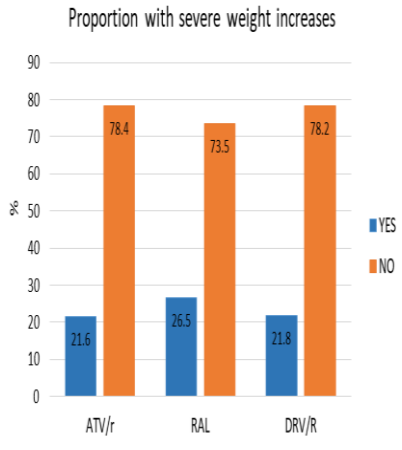
Effect is most pronounced with DTG, but also seen with RAL



Norwood et.al. 2017 JAIDS



Bhagwat et.al. 2017 CROI

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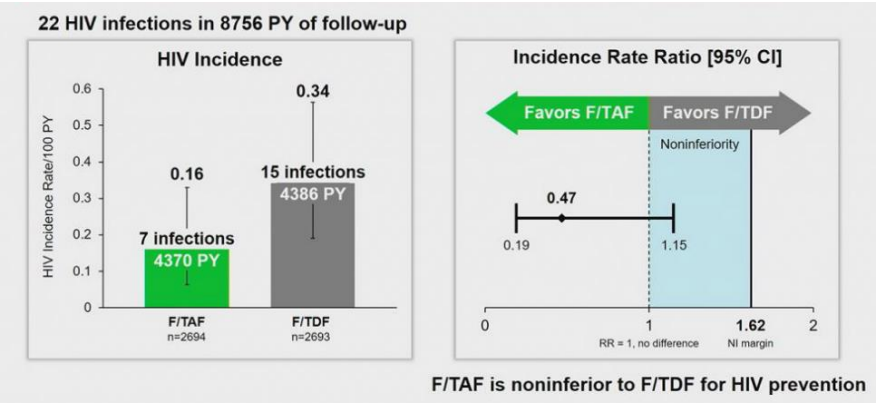
DISCOVER study suggests that TAF is non-inferior to TDF for PreP



Weight Gain
TAF = 1.1 kg
vs
TDF = 0.0 kg

Hare et al. CROI 2019 Seattle Abstract 104

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The current model of care is outdated

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New individualised models of care

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Multidisciplinary services are increasingly going to be needed

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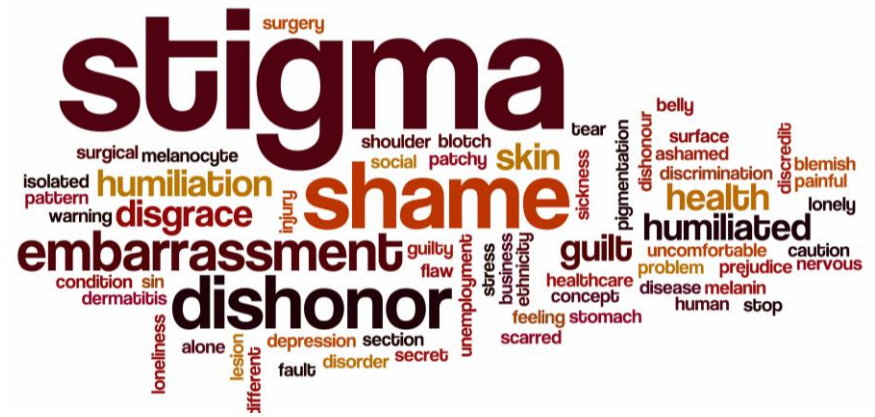
How do we tackle institutionalised stigma and discrimination?



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How do we ensure aged care that is sensitive to the needs of PWHIV?

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Summary

- New agents are promising particularly for heavily treatment experienced individuals
- Dual therapy regimens are options but need to carefully select suitable patients
- Injectable regimens seem efficacious but the question of who to use them in remains to be answered
- The demographic is changing and so how we provide care needs to as well

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