HIV Update

Chairs:

Dr Tristan Barber & Liz Foote

This educational event is supported by an unrestricted medical education grants from

GILEAD janssen MSD ViiV Healthcare

HIV update for Autumn BHIVA

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Disclosures & disclaimers

- Investigator on clinical trials sponsored by Janssen & Gilead
- Speaker/advisory fees: ViiV, Gilead, Janssen, MSD, Cipla & Mylan

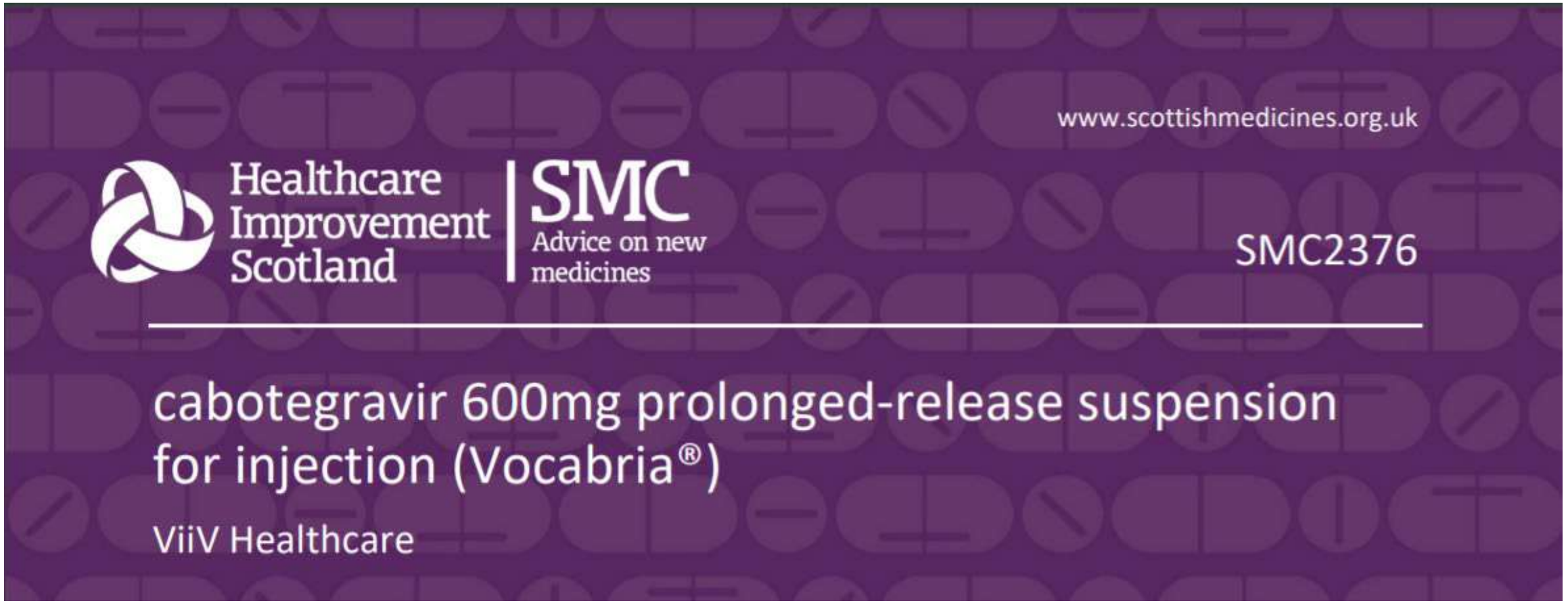
Most important disclosure

- You will have seen much of the data behind this talk ad nauseum
- Therefore my remit is to provoke thought & encourage all is us to QUESTION that data

Content

- Injectables
  - Scotland
  - England
- Pipeline
- The grand reveal (ish)

11th October 2021



Key points

- 74% predicted oral adherence in the model is not appropriate to people living with HIV in Scotland
- Additional benefit uncertain: SF-6D, an acceptable measure, may differ from more commonly used EQ-5D
- Potential issue as administration cost was based on 15 minutes of nurse time, most likely an underestimation
- **Could help remove the fear of hiding pill-based treatments and give greater freedom from rigorous treatment plans**

For every 50 patients on injectables we'll need to run an extra clinic a week

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Cabotegravir with rilpivirine for treating HIV-1

18 November 2021

Today's draft guidance is the first time NICE has made recommendations about the use of an HIV treatment since these came under NICE's remit in 2019.

It is estimated that around 13,000 people will now be eligible for treatment with cabotegravir with rilpivirine in England.

"We're pleased therefore to be able to recommend cabotegravir with rilpivirine as a valuable treatment option for people who already have good levels of adherence to daily tablets, but who might prefer an injectable regimen with less frequent dosing."

I have NEVER seen anything like it!

From: WATERS, Laura Jane (CENTRAL AND NORTH WEST LONDON NHS FOUNDATION TRUST) <lwaters@nhs.net>
Sent: 18 November 2021 11:49
Subject: [EXTERNAL]:URGENT: OMFG

I'm sure you appreciate the difficulty for surprised services dealing with multiple enquiries.

BHIVA shall indeed be reviewing vthe document in detail but I stand by my view that NICE could have made it clearer that the drugs are not available right now.

The 13,000 are total potentially eligible people that were estimated from the company originally. This is not the estimate of the number of people we expect to have treatment per year. Simply put, the true number of people receiving treatment will be much lower each year, and something we've had a dialogue with NHS England with.

If no appeals….statutory 3-month clock starts on 5th January 2022 to be implemented from April

Back to the NICE final appraisal document

Clinical trial results show that cabotegravir with rilpivirine is as effective as oral antiretrovirals at keeping the viral load lower than 50 copies/ml of blood. It is unclear whether there would be a difference in adherence between long-acting injections and daily oral tablets. The most likely cost-effectiveness estimate is likely to be within what NICE normally considers an acceptable use of NHS resources. So cabotegravir with rilpivirine is recommended.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/565621/2020
EMEA/H/C/004976

Vocabria (*cabotegravir*)

An overview of Vocabria and why it is authorised in the EU

EMA/565630/2020
EMEA/H/C/005060

Rekambys (*rilpivirine*)

2021 Calendar

January

S	M	T	W	T	F	S
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17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

February

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28						

March

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April

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June

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July

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August

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November

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December

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ViiV

Back to the NICE final appraisal document

Is it though?!

Clinical trial results show that cabotegravir with rilpivirine is as effective as oral antiretrovirals at keeping the viral load lower than 50 copies/ml of blood. It is unclear whether there would be a difference in adherence between long-acting injections and daily oral tablets. The most likely cost-effectiveness estimate is likely to be within what NICE normally considers an acceptable use of NHS resources. So cabotegravir with rilpivirine is recommended.

Summary of product characteristics

Prior to starting REKAMBYS, the healthcare professional should carefully select patients who agree to the required injection schedule and counsel patients about the importance of adherence to scheduled dosing visits to help maintain viral suppression and reduce the risk of viral rebound and potential development of resistance associated with missed doses.

2 of these factors = more VF

Proviral RPV RAMs

Subtype A6/A1 (assoc with L74I)

BMI ≥30 (assoc with CAB PK)

ATLAS-2M week 48

CVF: 1.5% on Q8W & 0.4% on Q4W

RAMs: 1% on Q8W, 0.4% on Q4W

Overall Summary of CVFs through Week 96

	n	CVFs n (%)	CVFs with RPV RAMs*	RPV RAMs observed at failure	CVFs with IN RAMs*	IN RAMs observed at failure
Q8W	522	[illegible] (1.[illegible]	[illegible]7/9	K[illegible] E[illegible]3E[illegible], [illegible]38[illegible] Y1[illegible]L, Y1[illegible]C	[illegible]5/9	Q1[illegible]R,† N155H†
Q4W	523	2 (0.4)	1/2	K101E, M230L	2/2	E138E/K, Q148R, N155N/H

100% ADHERENCE

CUSTOMIZE

Phase IIIb, hybrid III implementation-effectiveness study of monthly CAB/RPV

Virologic Outcome at Month 12, n (%)	Patients (N = 115)
Virologic success (<50 copies/mL)	101 (88)
Virologic nonresponse (≥50 copies/mL)	0
No virologic data ▪ Discontinued due to AE or death ▪ Discontinued for other reasons ▪ On study but missing data in window	14 (12) 5 (4)* 8 (7) 1 (1)†
Scheduling injection visits	2

2% withdrew for ISR

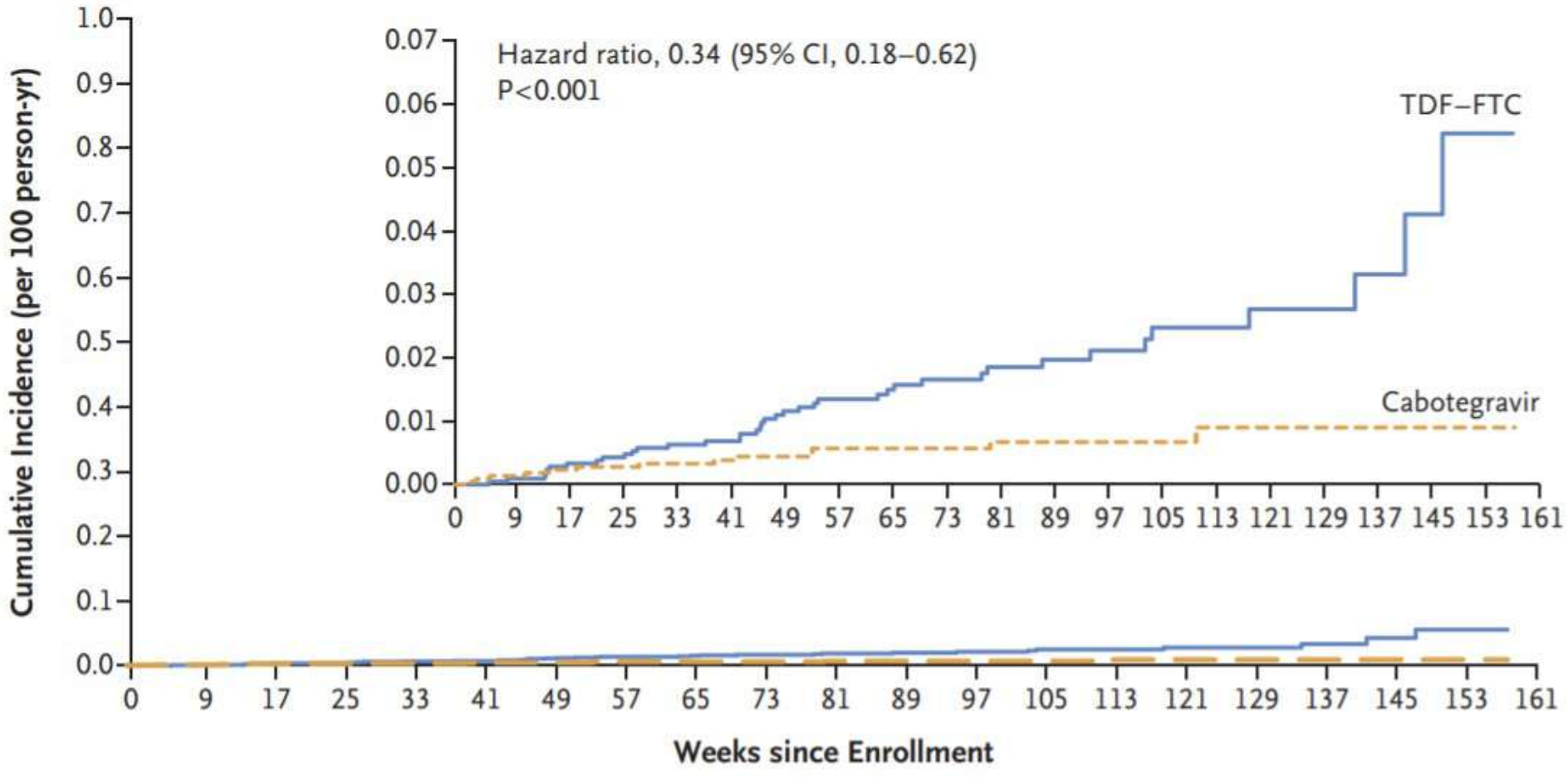
Time in clinic:

- Month 1: 57 min
- Month 11: 34 min

Czarnogorski M et al. IAS 2021. Abstr OAD0705.

Slide adapted from: clinicaloptions.com

HPTN 083: IM CAB vs TDF/FTC



No. at Risk

TDF–FTC	2281	2132	2081	2019	1913	1765	1624	1494	1295	1132	965	817	644	517	401	311	231	150	85	33	0
Cabotegravir	2280	2138	2091	2031	1920	1776	1633	1489	1315	1124	957	798	644	503	401	318	243	173	111	42	0

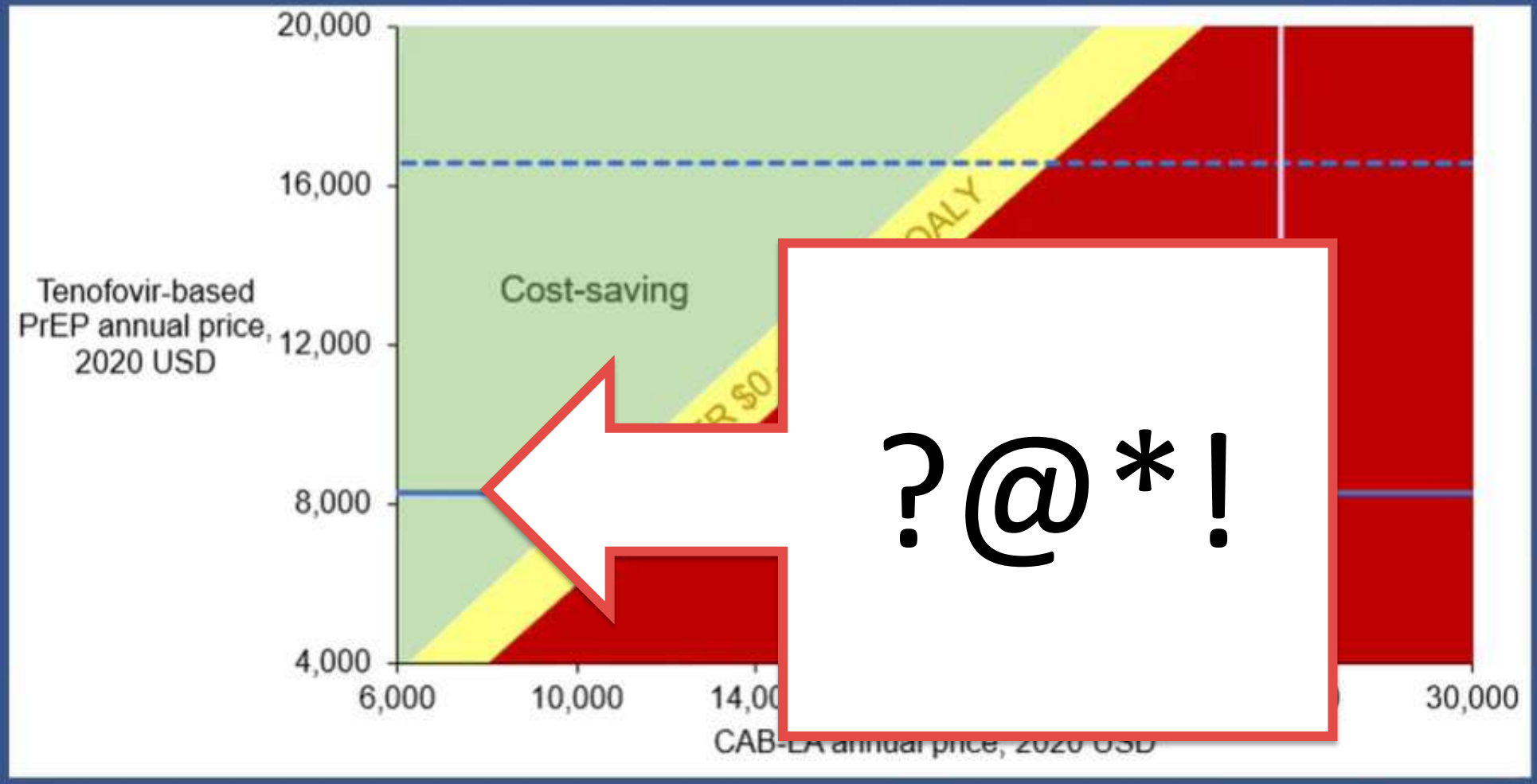
Landovitz RJ et al. N Engl J Med 2021;385:595-608

Crucial point

- **Adherence**
  - IM CAB 92%
  - PO TDF/FTC 74% had PK consistent with daily dosing
- **Incident HIV infections**
  - IM CAB: 4/12 with target plasma CAB concentrations & on-time dosing
  - TDF/FTC: 37/39 had suboptimal or non-adherence

Landovitz RJ et al. N Engl J Med 2021;385:595-608

Sensitivity analysis: PrEP drug prices



No plans for Descovy PrEP in the EU

Gilead Announces Decision Not to Pursue Marketing Authorization for Descovy® for Pre-Exposure Prophylaxis in the European Union

Foster City, Calif., October 20, 2021 –Gilead today announced it will not pursue a marketing authorization for Descovy®(emtricitabine 200 mg/tenofovir alafenamide 25 mg) for pre-exposure prophylaxis (PrEP) in the European Union (EU) at this time. Conversations with healthcare professionals, payers and other stakeholders across Europe have confirmed there is a lack of demand for innovative daily PrEP options given the broad availability of generic alternatives. Policies and decisions made by national governments relating to reimbursement can adversely impact the feasibility of pursuing marketing authorization in each market. This is the case in the EU.

https://www.gilead.com/news-and-press/company-statements/gilead-announces-decision-not-to-pursue-marketing-authorization-for-descovy-for-pre-exposure-prophylaxis-in-the-european-union accessed 11/11/21

Medicines & Healthcare products Regulatory Agency

The pipeline is a bit smaller than it was

- **MK-8507**
  - Decreases in TLC & CD4 on islatravir (ISL) + MK-8507
  - External Data Monitoring Committee (eDMC):
    - Effect related to the **combination** of ISL+MK-8507;
    - Greatest decreases on highest doses of MK-8507
    - Recommended trial cessation
  - MSD announced on 18th November 2021
    - Paused development of MK-8507
    - Remains confident in ISL

Maybe not all that confident?

Gilead and Merck Announce Temporary Pause in Enrollment fo… …ing an Oral Weekly … …tional Islatra…

Foster …ead Sciences, …tates and Canada, are t… …2 clinical study (NCT0505299… …gational once-weekly oral combination treatment …gimen of islatravir and lenacapavir in people living with HIV who are virologically suppressed on antiretroviral

Paused due to an "abundance of caution"

Press release 23rd November 2021

ViiV
PARTY

IL-6 & SNAE risk: 2DR vs 3DR

Markov modelling from TANGO & AIR

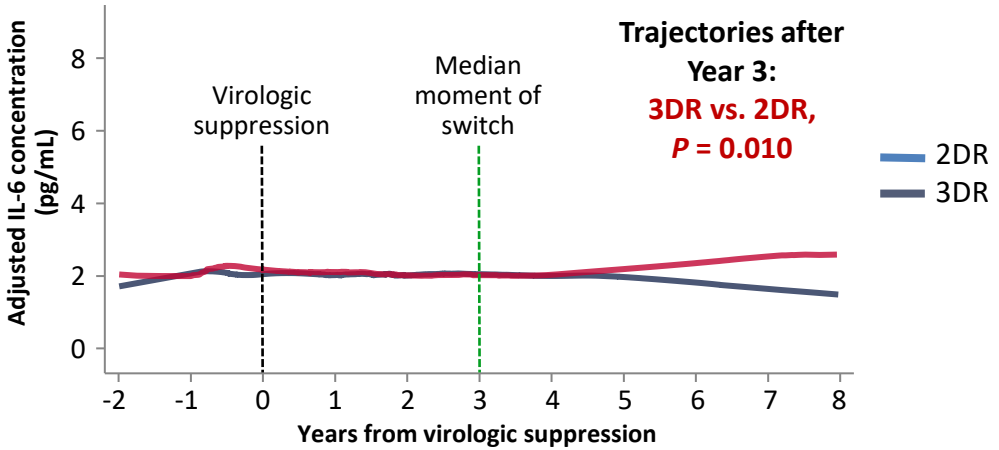
The INSIGHT trials network showed that elevated inflammatory markers (including IL-6) are associated with a higher risk of SNAE or death*,[1]

- Findings predicted that **a 16% increase in IL-6 may increase the risk of SNAE by ~16%** – the difference in IL-6 level observed in TANGO at Week 48

IL-6 Levels in TANGO and SALSA Studies

Study	Switch	Change in IL-6 level after switching from 3DR to 2DR	
TANGO	Switch to DTG/3TC vs. continuing a TAF-based 3DR	Week 48	*P* = 0.006 in favor of 3DR[2]
		Week 96	Numerical difference but not statistically significant[3]
		Week 144	*P* = 0.039 in favor of 3DR[4]

AIR: Serum IL-6 After Switching From 3DR to 2DR[6]



*Cardiovascular, hepatic, renal or malignancy event

1. Grund B, et al. PLoS One 2016; 2. van Wyk J, et al. Clin Infect Dis 2020; 3. Wang R, et al. IAS 2021, OAB0301; 4. Osiyemi O, et al. ID Week 2021, Poster 900; 5. Llibre JM, et al. IAS 2021, OALB0303; 6. Serrano-Villar S, et al. AIDS 2020, OAB030; 7.Serrano Villar S, et al. EACS 2021, PE2/34

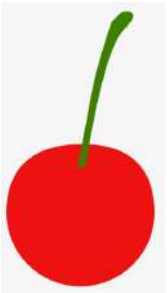
On vs off ART comparisons

% vs absolute value?

Confounders? Adherence, statins

Causation vs association

MAJOR ARTICLE



Plasma Levels of Soluble CD14 Independently Predict Mortality in HIV Infection

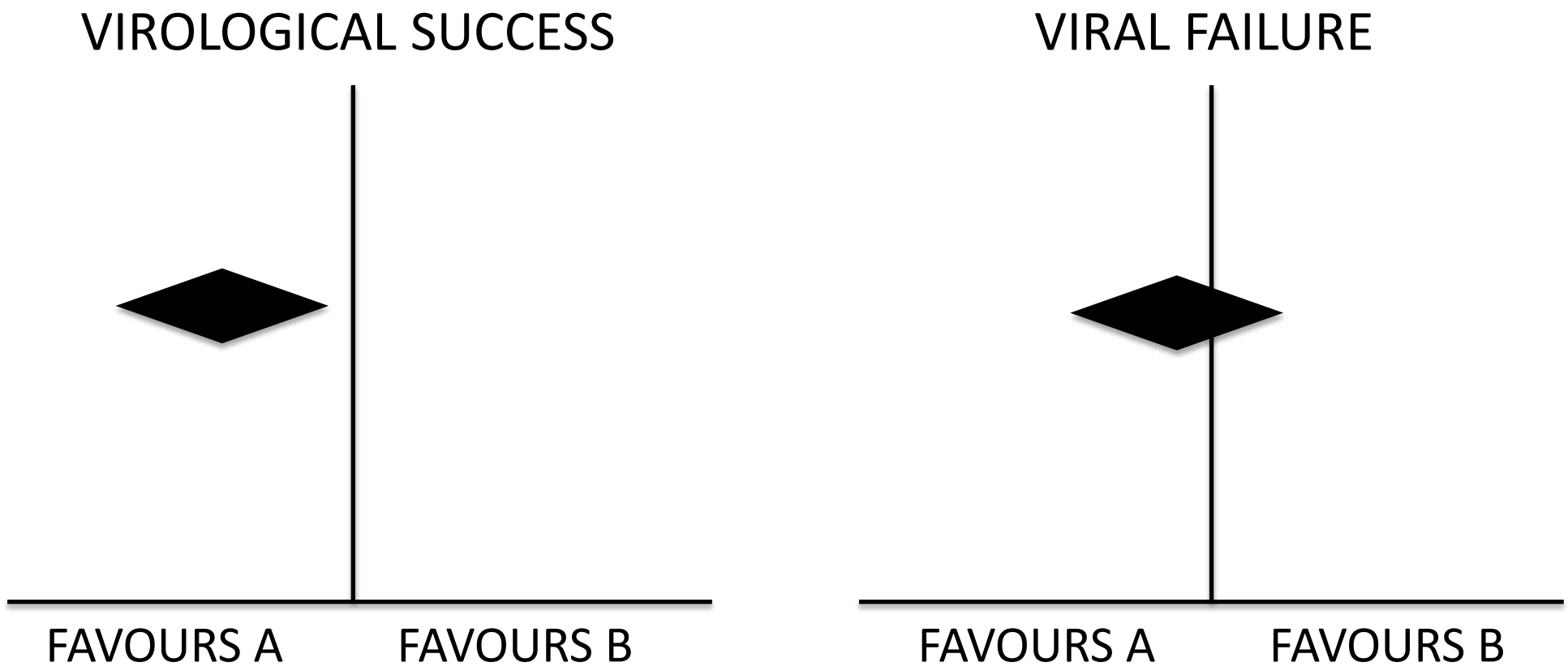
Netanya G. Sandler,[1] Handan Wand,[10] Annelys Roque,[1] Matthew Law,[10] Martha C. Nason,[3] Daniel E. Nixon,[5] Court Pedersen,[8] Kiat Ruxrungtham,[9] Sharon R. Lewin,[11,12,13] Sean Emery,[10] James D. Neaton,[6] Jason M. Brenchley,[2] Steven G. Deeks,[7] Irini Sereti,[4] and Daniel C. Douek,[1] for the INSIGHT SMART Study Group

BHIVA
British HIV Association
GUIDELINES

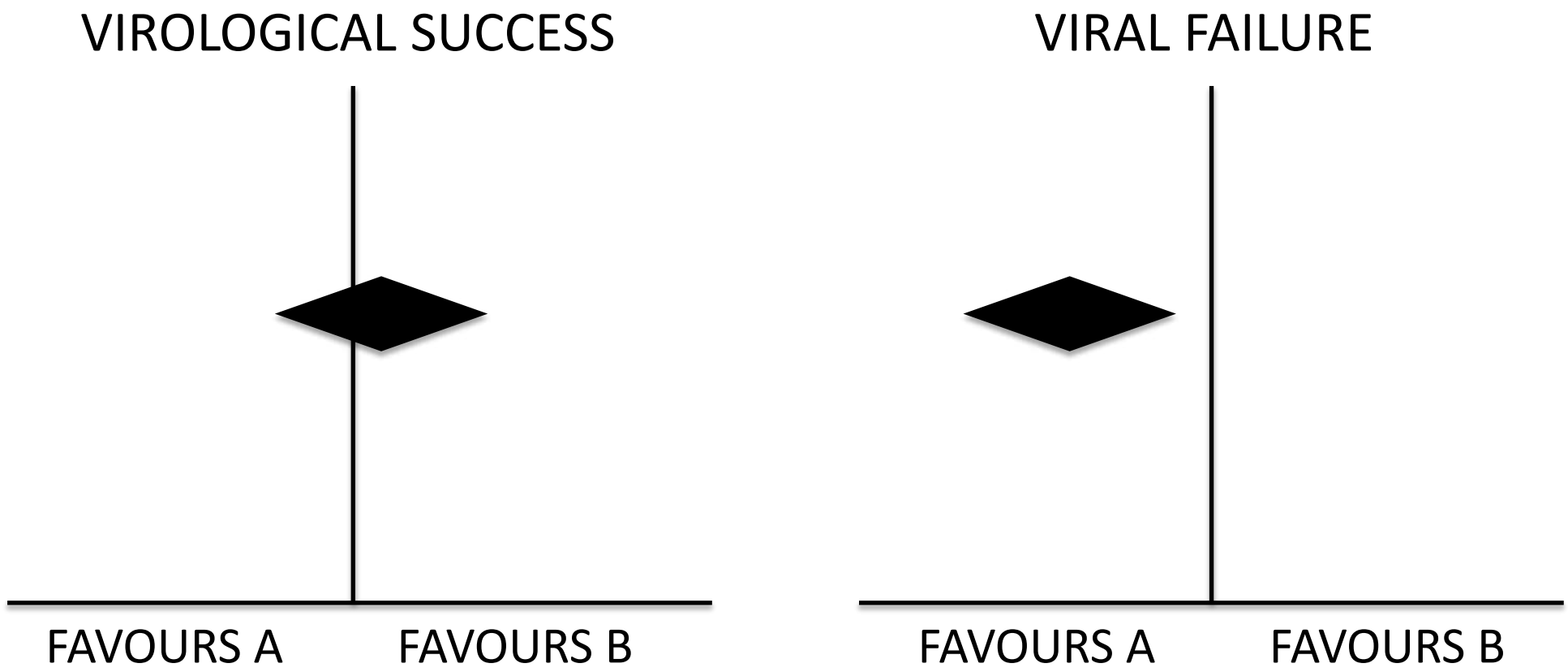
Recommended 1st line regimens

Bictegravir/emtricitabine/tenofovir-AF Dolutegravir/abacavir/lamivudine Dolutegravir + emtricitabine/tenofovir-AF Dolutegravir + emtricitabine/tenofovir-DX Dolutegravir/lamivudine Raltegravir + emtricitabine/tenofovir-AF Raltegravir + emtricitabine/tenofovir-DF	Doravirine/lamivudine/tenofovir-DF Doravirine + emtricitabine/tenofovir-AF Darunavir/b + emtricitabine/tenofovir-AF Darunavir/b + emtricitabine/tenofovir-DF

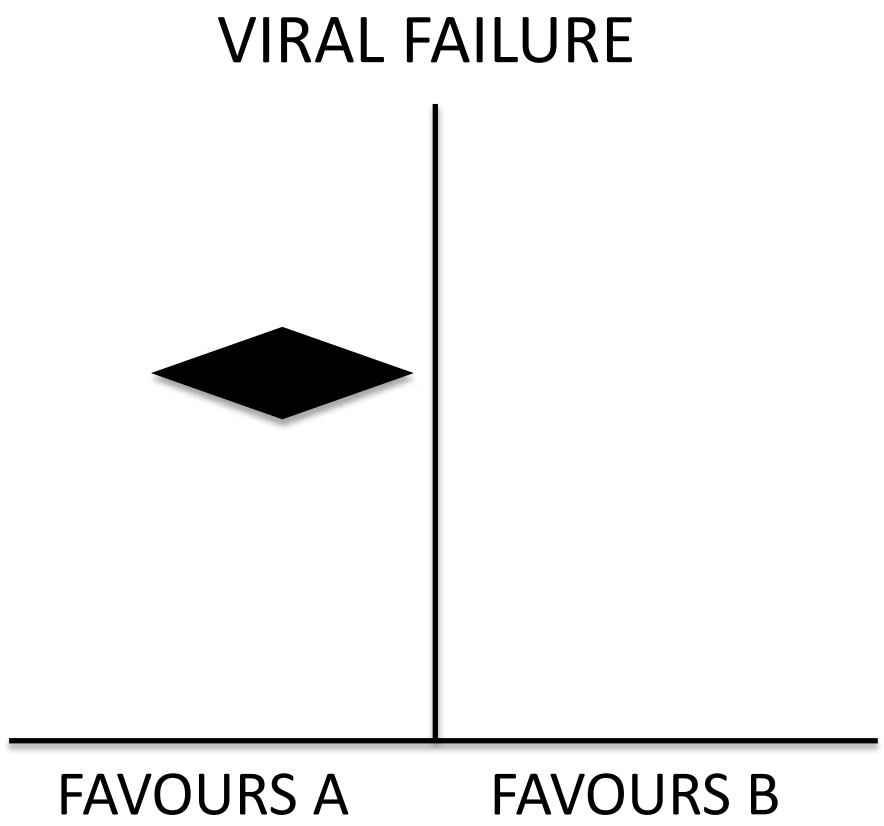
Regimen A vs regimen B

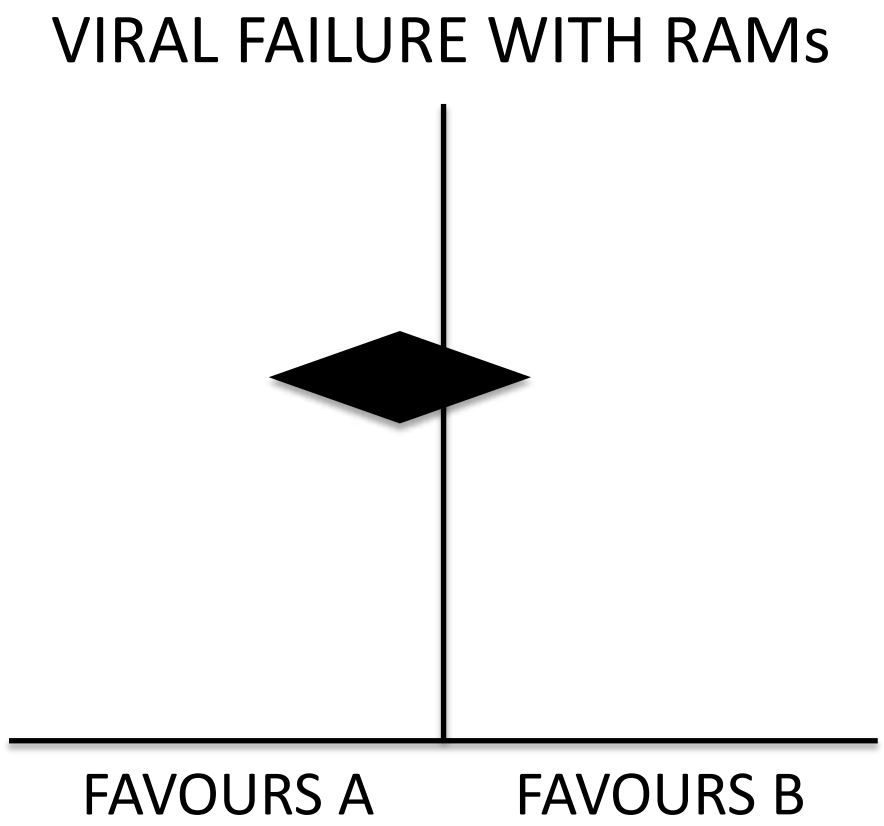


Regimen A vs regimen B



Regimen A vs regimen B





Conclusions

- Injectables are here
  - We must ensure those in greatest need get access
  - We must manage expectations realistically
- New drugs can still stutter
- Interpret single biomarker extrapolations cautiously
- BHIVA ART guidelines out for consultation soon

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Thank you!

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@drlaurajwaters