# TAF-Based Regimens to Achieve Long Term Treatment Success

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ORIGINAL RESEARCH

*Journal of Virus Eradication* 2018; **4**: 72–79

# Tenofovir alafenamide versus tenofovir disoproxil fumarate: is there a true difference in efficacy and safety?

Andrew Hill[1]*, Sophie L Hughes[2], Dzintars Gotham[2] and Anton L Pozniak[3]

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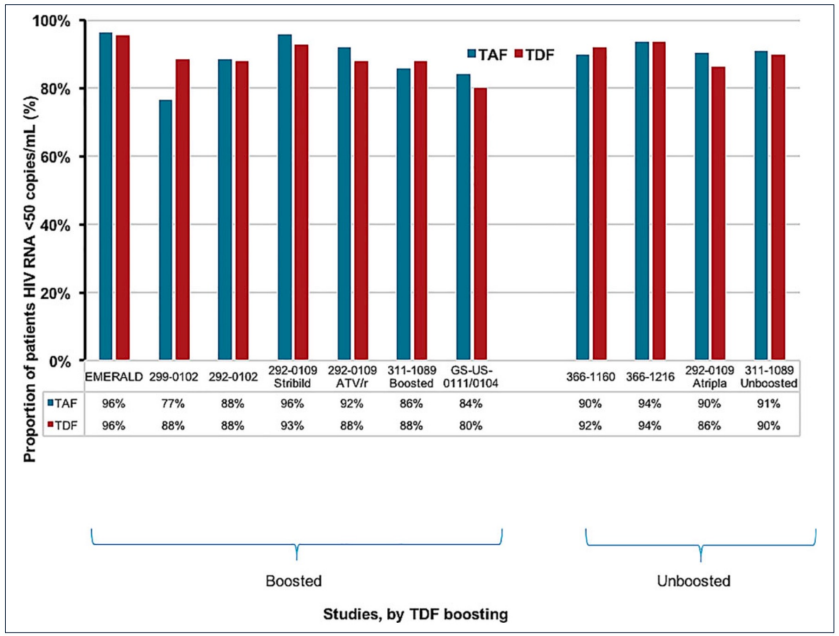
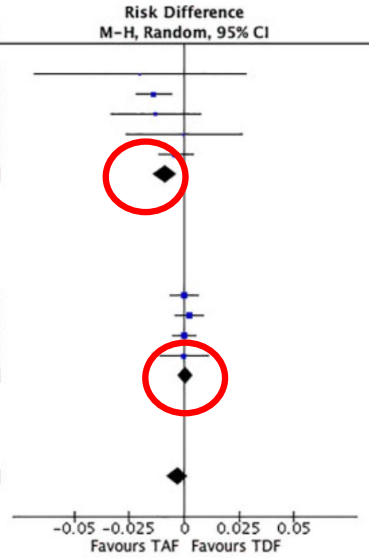
[3] Chelsea and Westminster Hospital NHS Foundation Trust, London, UK



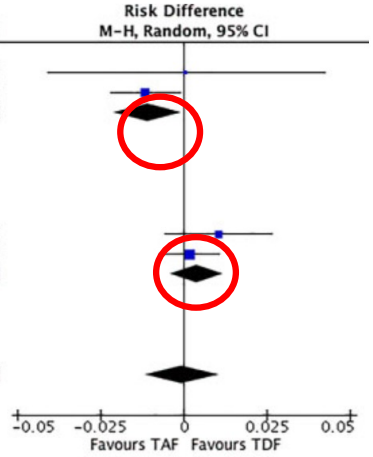
(b) Study discontinuations due to renal adverse events

| Study or Subgroup | TAF Events | TAF Total | TDF Events | TDF Total | Weight | Risk Difference M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **23.1.1 Boosted** | | | | | | |
| GS-US-299-0102 | 0 | 103 | 1 | 50 | 1.0% | -0.02 [-0.07, 0.03] |
| GS-US-292-0111 and GS-US-292-0104 pooled | 0 | 866 | 12 | 867 | 14.2% | -0.01 [-0.02, -0.01] |
| GS-US-292-0109 Stribild Switch | 0 | 306 | 2 | 153 | 4.7% | -0.01 [-0.03, 0.01] |
| GS-US-292-0102 | 0 | 112 | 0 | 58 | 3.1% | 0.00 [-0.03, 0.03] |
| EMERALD | 1 | 763 | 2 | 378 | 14.7% | -0.00 [-0.01, 0.00] |
| **Subtotal (95% CI)** | | **2150** | | **1506** | **37.6%** | **-0.01 [-0.01, -0.00]** |
| Total events | 1 | | 17 | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.18$, df = 4 (P = 0.38); $I^2 = 4\%$ | | | | | | |
| Test for overall effect: Z = 3.11 (P = 0.002) | | | | | | |
| **23.1.2 Unboosted** | | | | | | |
| GS-US-366-1216 | 0 | 316 | 0 | 314 | 16.8% | 0.00 [-0.01, 0.01] |
| GS-US-366-1160 | 1 | 438 | 0 | 437 | 16.7% | 0.00 [-0.00, 0.01] |
| GS-US-320-0110 | 0 | 582 | 0 | 292 | 18.1% | 0.00 [-0.01, 0.01] |
| GS-US-320-0108 | 0 | 285 | 0 | 140 | 10.8% | 0.00 [-0.01, 0.01] |
| **Subtotal (95% CI)** | | **1621** | | **1183** | **62.4%** | **0.00 [-0.00, 0.00]** |
| Total events | 1 | | 0 | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.38$, df = 3 (P = 0.94); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 0.36 (P = 0.72) | | | | | | |
| **Total (95% CI)** | | **3771** | | **2689** | **100.0%** | **-0.00 [-0.01, 0.00]** |
| Total events | 2 | | 17 | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 19.57$, df = 8 (P = 0.01); $I^2 = 59\%$ | | | | | | |
| Test for overall effect: Z = 1.18 (P = 0.24) | | | | | | |
| Test for subgroup differences: $Chi^2 = 8.23$, df = 1 (P = 0.004), $I^2 = 87.8\%$ | | | | | | |




(c)Bone fracture events

| Study or Subgroup | TAF Events | TAF Total | TDF Events | TDF Total | Weight | Risk Difference M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **12.1.1 Boosted** | | | | | | |
| GS-US-292-0102 | 2 | 112 | 1 | 58 | 6.2% | 0.00 [-0.04, 0.04] |
| GS-US-292-0111 and GS-US-292-0104 pooled | 6 | 866 | 16 | 867 | 33.4% | -0.01 [-0.02, -0.00] |
| **Subtotal (95% CI)** | | **978** | | **925** | **39.6%** | **-0.01 [-0.02, -0.00]** |
| Total events | 8 | | 17 | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.31$, df = 1 (P = 0.58); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 2.07 (P = 0.04) | | | | | | |
| **12.1.2 Unboosted** | | | | | | |
| GS-US-320-0108 | 3 | 285 | 0 | 140 | 23.8% | 0.01 [-0.01, 0.03] |
| GS-US-320-0110 | 3 | 581 | 1 | 292 | 36.6% | 0.00 [-0.01, 0.01] |
| **Subtotal (95% CI)** | | **866** | | **432** | **60.4%** | **0.00 [-0.00, 0.01]** |
| Total events | 6 | | 1 | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.92$, df = 1 (P = 0.34); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 0.96 (P = 0.34) | | | | | | |
| **Total (95% CI)** | | **1844** | | **1357** | **100.0%** | **-0.00 [-0.01, 0.01]** |
| Total events | 14 | | 18 | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.20$, df = 3 (P = 0.07); $I^2 = 58\%$ | | | | | | |
| Test for overall effect: Z = 0.12 (P = 0.91) | | | | | | |
| Test for subgroup differences: $Chi^2 = 4.97$, df = 1 (P = 0.03), $I^2 = 79.9\%$ | | | | | | |



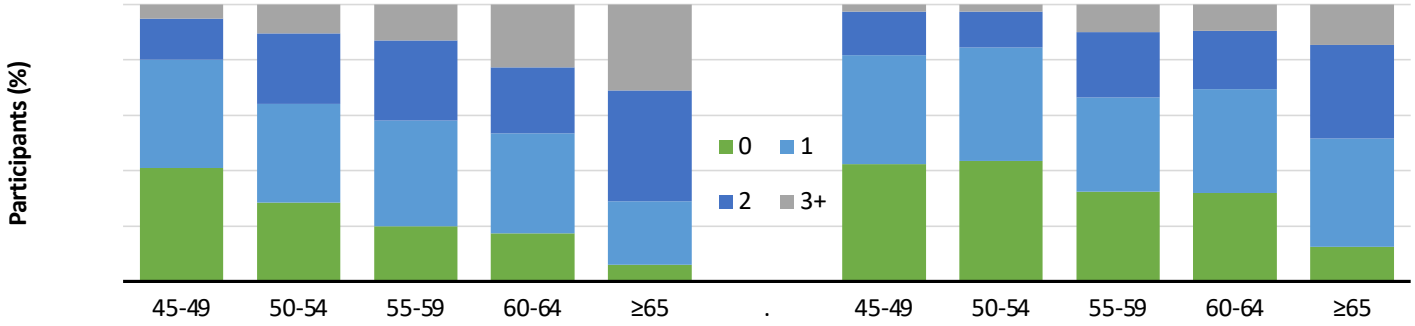
# What does this mean in clinical practice in 2022?

# Co-morbidities are prevalent among ageing PLWHIV

***AANCC incidence stratified by age in the AGE$_h$IV Cohort Study, 2010–2012***

HIV-infected (N=540)
Mean AANCC/person = 1.3 (SD 1.14)

HIV-uninfected controls (N=524)
Mean AANCC/person = 1.0 (SD 0.96)

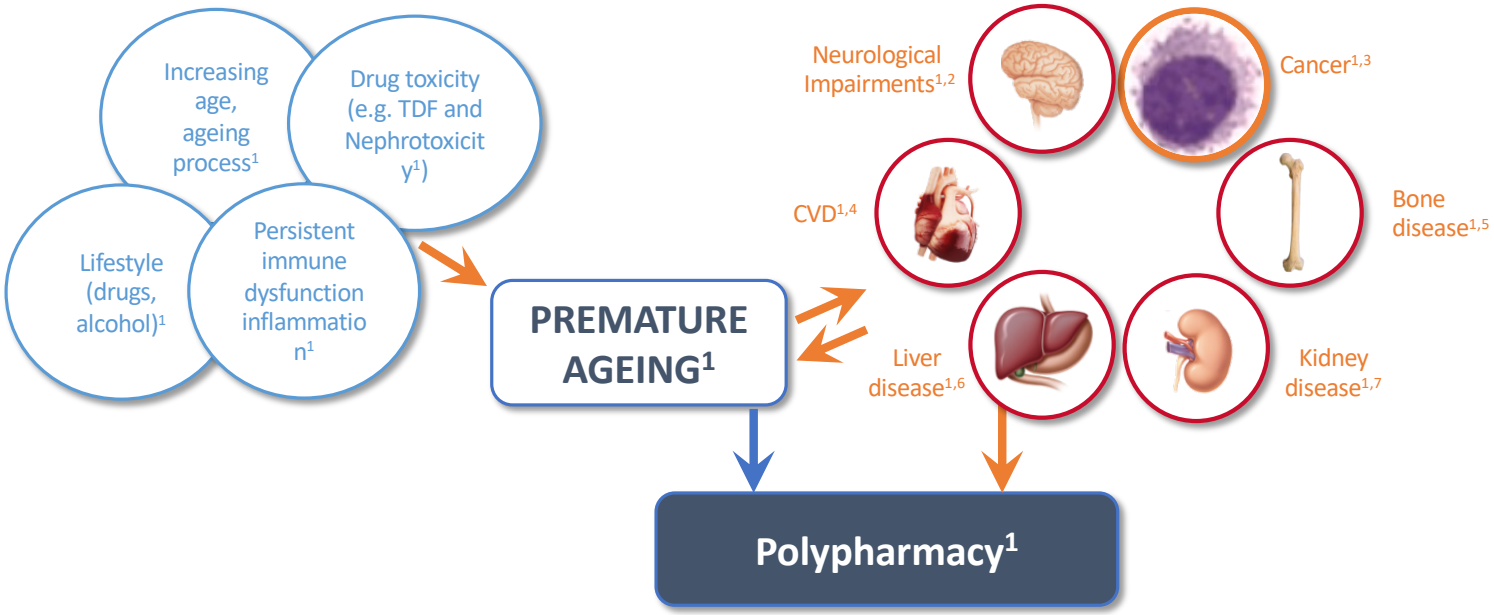



| Age (years) | 45–49 | 50–54 | 55–59 | 60–64 | ≥65 | | 45–49 | 50–54 | 55–59 | 60–64 | ≥65 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mean number of AANCC | 0.83 | 1.18 | 1.34 | 1.52 | 1.96 | | 0.79 | 0.75 | 1.11 | 1.08 | 1.51 |
| Number of participants | 184 | 126 | 97 | 58 | 55 | | 193 | 130 | 84 | 66 | 41 |

AANCC, age-associated non-communicable co-morbidities

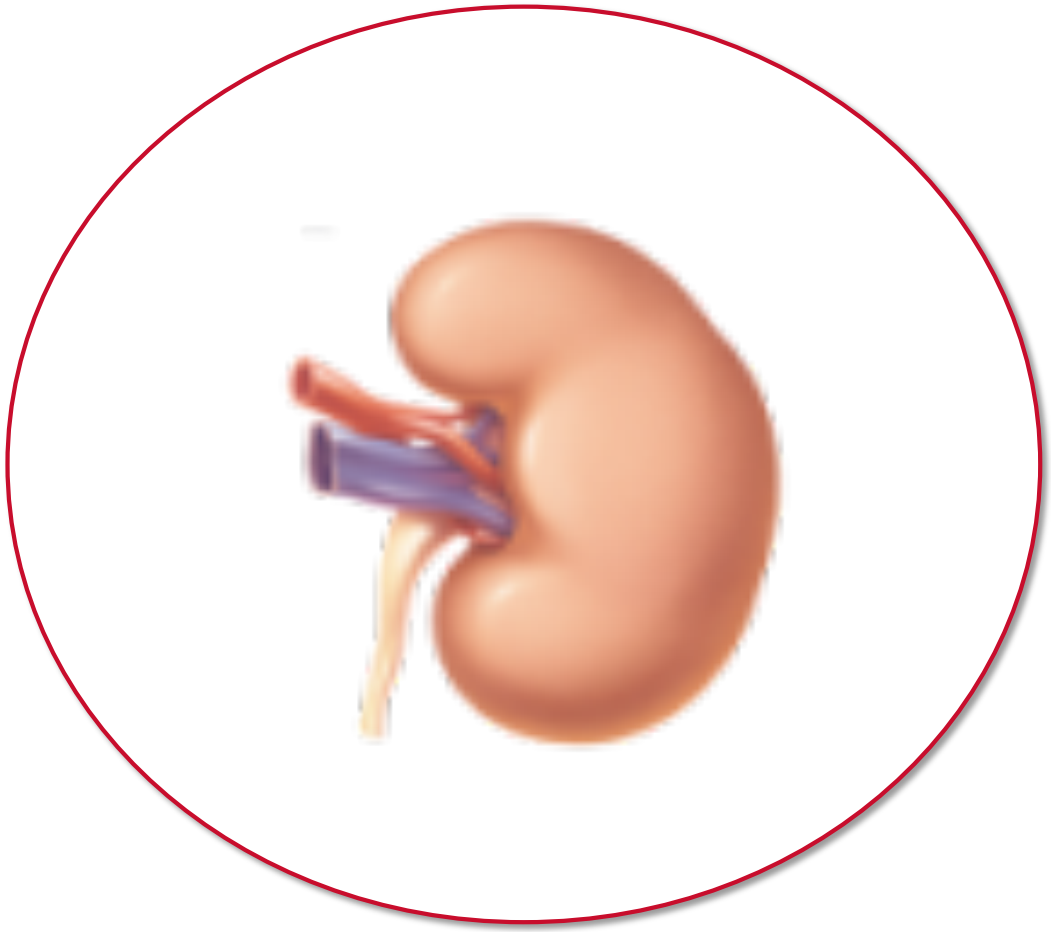
Schouten J et al. Clin Infect Dis 2014:59:1787–97

# Do patients with HIV age prematurely?





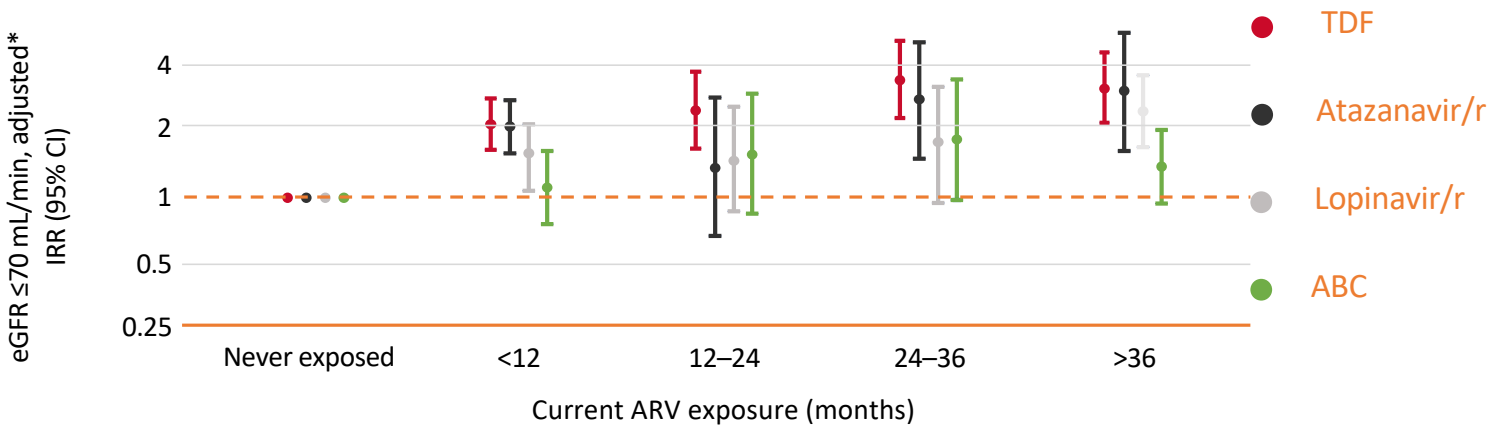
1. Deeks SG et al. BMJ 2009;338:a3172
2. McArthur JC et al. Ann Neurol 2010;67:699–714
3. Nguyen ML et al. 18th IAC. Vienna, Austria 2010. Abstract WEAB0105
4. Freiberg MS et al. JAMA Intern Med 2013;173:614–22
5. Brown TT et al. AIDS 2006;20:2165–74
6. Towner WJ et al. JAIDS 2012;60:321–7
7. Lucas GM et al. Clin Infect Dis 2014;59



# The risk of renal complications can be increased by some ART options

## D:A:D Study: Some HIV treatments exacerbate the decline of renal function over time[1]

*Comparison of estimated glomerular filtration rates by ARV exposure[2]*




*Adjusted for baseline estimated glomerular filtration rate (eGFR), age, gender, race, HIV risk group, enrolment cohort, CD4 nadir, and baseline date. AIDS, HBV/HCV status, smoking status, hypertension, diabetes, CV event, CD4, VL, and cumulative exposure to indinavir, unboosted atazanavir, and other boosted PIs (darunavir, tipranavir, (fos)amprenavir) (included as time-updated variables)

TDF, Tenofovir; r, Ritonavir; ABC, Abacavir

Ryom L et al. J Infect Dis 2013;207(9):1359–69

# TAF – containing cART

**Descovy**

**Odefsey**

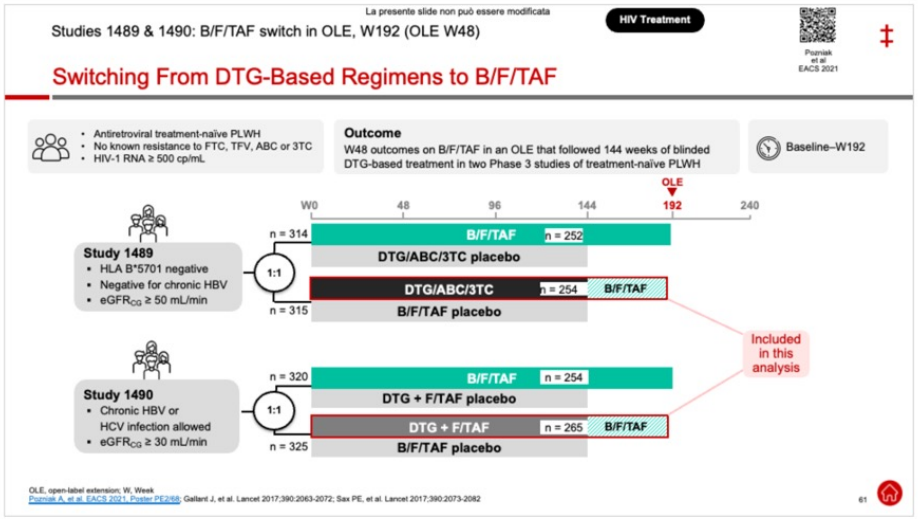
**Symtuza**

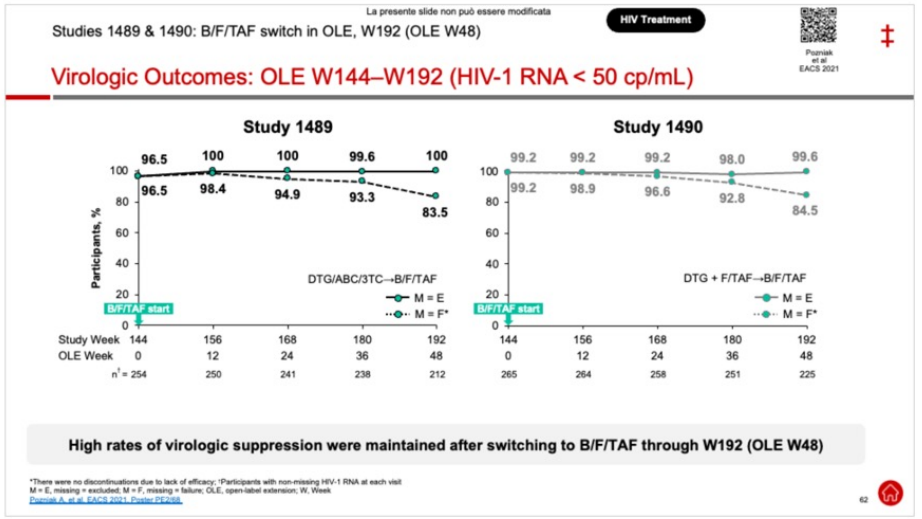
**Biktavy**

**Genvoya**

Studies 1489 & 1490: B/F/TAF switch in OLE, W192 (OLE W48)

# Studies 1489 & 1490: Study Design and Virologic Outcomes




**4 year data**

OLE, open-label extension; W, Week
Pozniak A, et al. EACS 2021, Poster PE2/68
Gallant J, et al. Lancet 2017;390:2063-2072
Sax PE, et al. Lancet 2017;390:2073-2082

Studies 1489 & 1490: B/F/TAF switch in OLE, W192 (OLE W48)

# Resistance Outcomes Through W192

| | Baseline–W144 | | W144–Unblinding | | OLE B/F/TAF | |
|---|---|---|---|---|---|---|
| **Participants, n** | DTG/ABC/3TC n = 315 | DTG + F/TAF n = 325 | DTG/ABC/3TC n = 269 | DTG + F/TAF n = 281 | DTG/ABC/3TC→ B/F/TAF n = 254 | DTG + F/TAF→ B/F/TAF n = 265 |
| Met criteria for resistance testing* | 6 | 7 | 4 | 1 | 1 | 1 |
| NRTI resistance detected | 0 | 0 | 2 (M184V) | 0 | 0 | 0 |
| INSTI resistance detected | 0 | 0 | 0 | 0 | 0 | 0 |

**After W144, but prior to switch, two participants on blinded study drug of DTG/ABC/3TC developed M184V, switched to B/F/TAF and achieved HIV-1 RNA < 50 cp/mL at their next visit**

**No cases of treatment-emergent resistance to any of the components of B/F/TAF through 48 weeks OLE (study W192)**

*Resistance testing performed for participants with confirmed HIV-1 RNA ≥ 200 cp/mL or ≥ 200 cp/mL at last visit, with no resuppression of HIV-1 RNA to < 50 cp/mL while on study drug
OLE, open-label extension; W, Week
Pozniak A, et al. EACS 2021. Poster PE2/68

Studies 1489 & 1490: B/F/TAF switch in OLE, W192 (OLE W48)

# AEs and Laboratory Abnormalities: OLE W144 to W192

| | DTG/ABC/3TC→ B/F/TAF n = 254 | DTG + F/TAF→ B/F/TAF n = 265 |
|---|---|---|
| Any study drug–related AEs | 3% | 2% |
| AEs leading to discontinuation | 1* | 0 |
| Any Grade 3/4 laboratory abnormality | 8% | 14% |
| Non-fasting hyperglycemia | 1% | 3% |
| Increased fasting LDL | 1% | 3% |
| Glycosuria | 1% | 2% |

**Nausea and diarrhea**

Incidence and prevalence declined numerically after switching to B/F/TAF in the OLE

**Renal safety**

- 0 cases of proximal renal tubulopathy
- 0 discontinuations due to renal AEs

**Fasting lipid changes**

- Small changes in lipid fractions
- Initiated lipid-lowering therapy after switch:
  - Study 1489: 2%; Study 1490: 4%

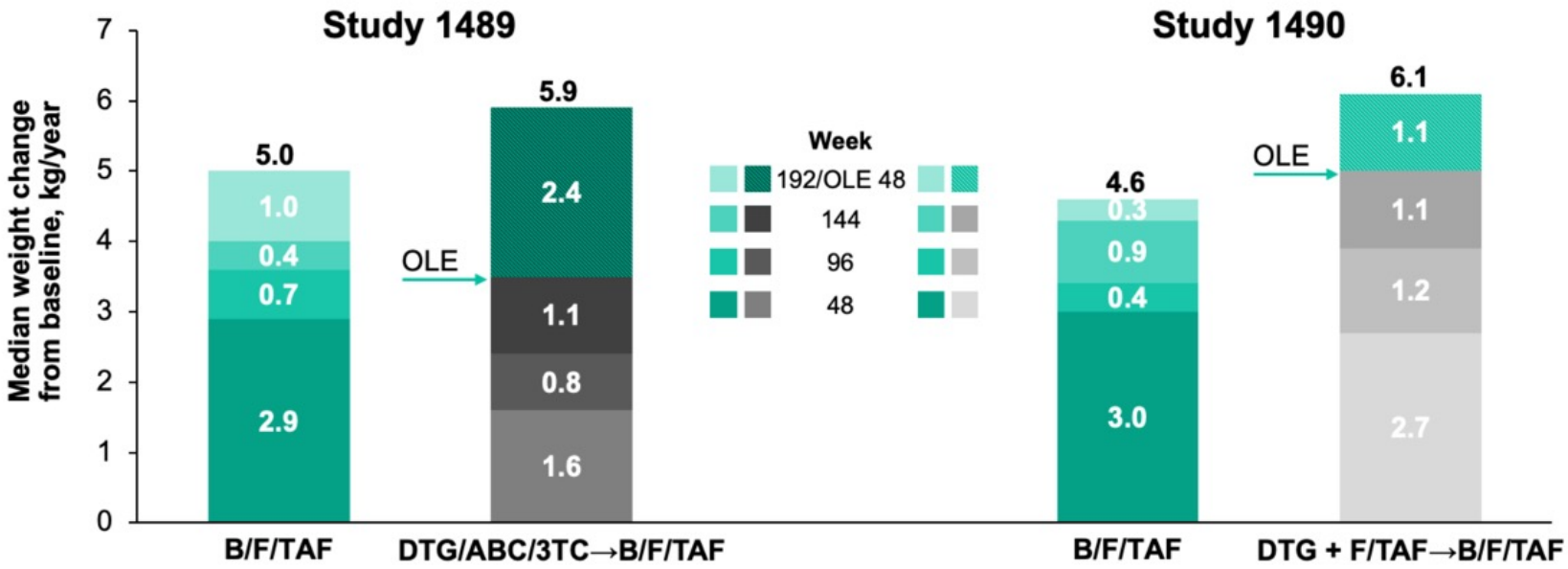
**Switch to B/F/TAF was generally well tolerated, with few drug-related AEs through OLE W48 (Study W192)**
**No reported cases of proximal renal tubulopathy or discontinuations due to renal AEs**

*1 participant died due to seizure unrelated to study drug on OLE Day 335/Study Week 192
OLE, open-label extension; W, Week
Pozniak A, et al. EACS 2021. Poster PE2/68

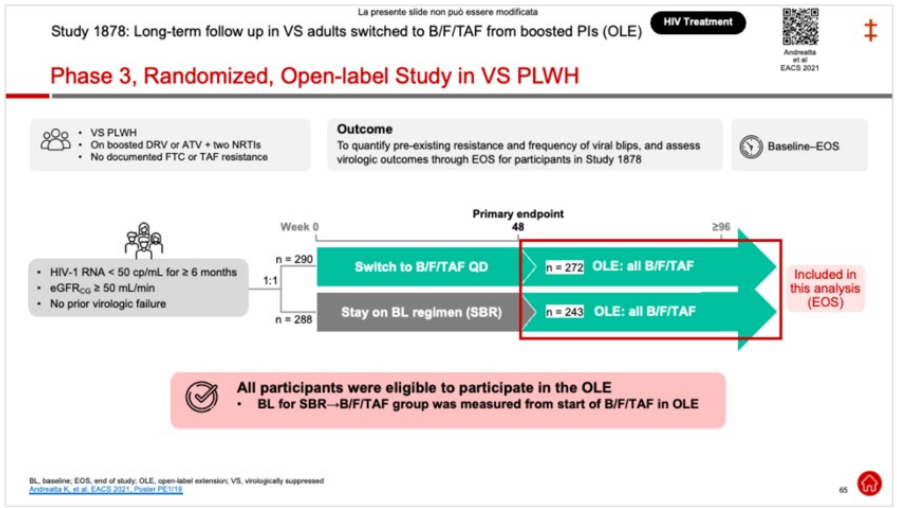
# Weight gain

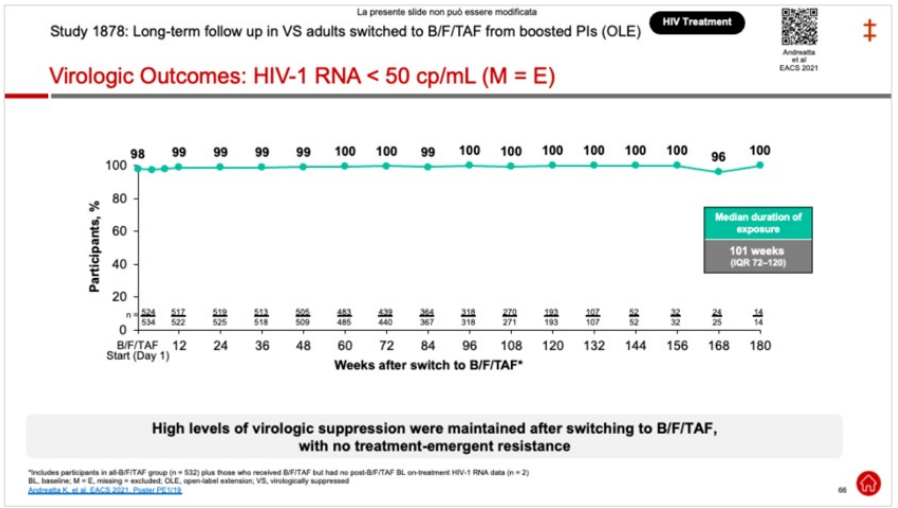
## Annual Median Weight Change From Baseline Through W192

EACS 2021



# Study 1878: Study Design and Virologic Outcomes

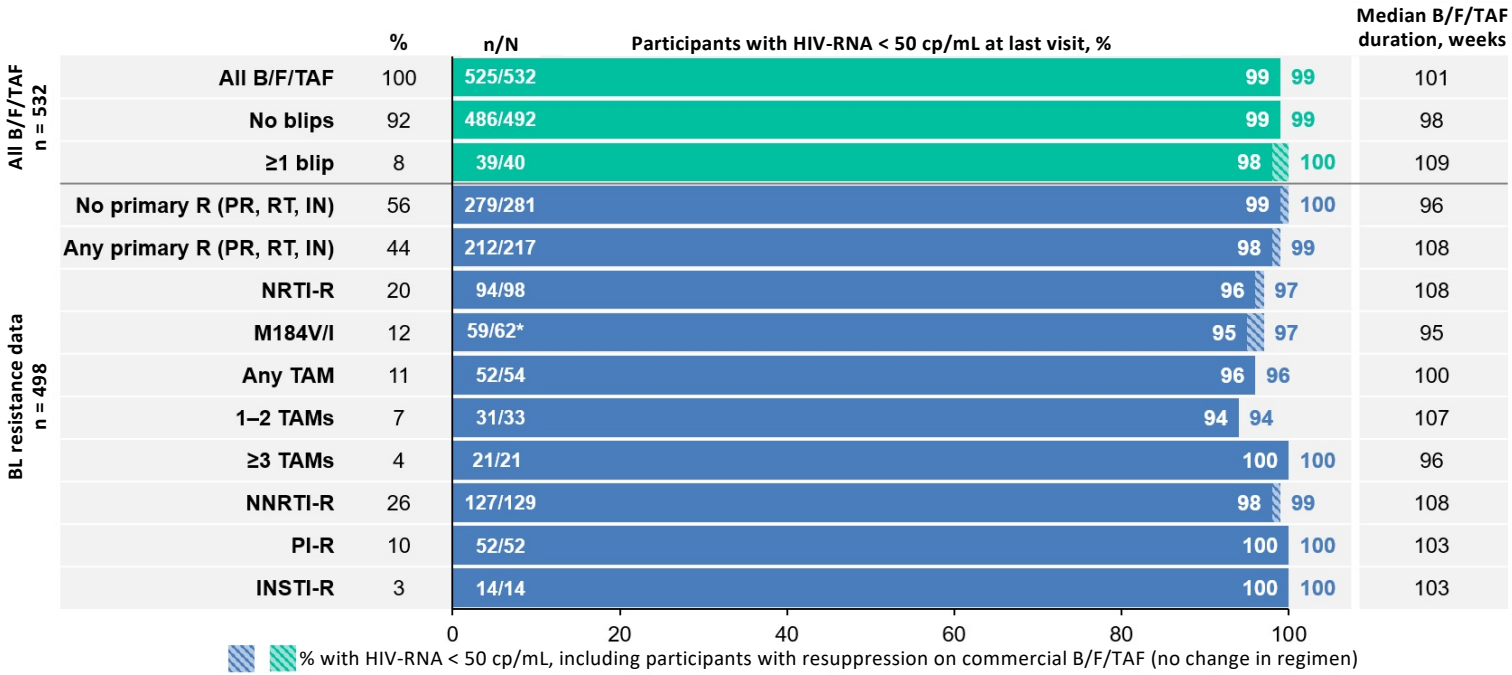



OLE, open-label extension; VS, virologically suppressed
Andreatta K, et al. EACS 2021. Poster PE1/19

Study 1878: Long-term follow up in VS adults switched to B/F/TAF from boosted PIs (OLE)

# Virologic outcomes by blips and baseline resistance



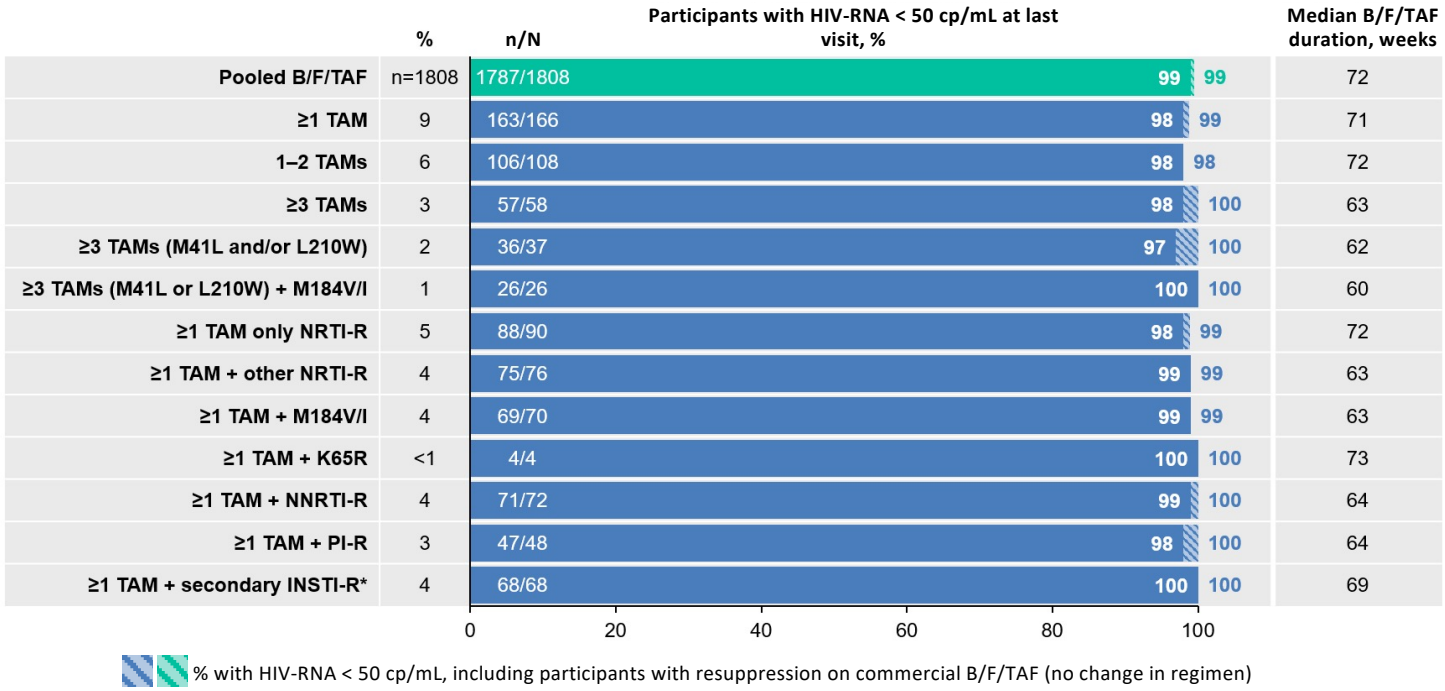

Blips of HIV-1 RNA ≥ 200 cp/mL were associated with lower adherence

**High rates of virologic suppression were maintained after switching to B/F/TAF, regardless of pre-existing resistance or blip**

*Of three participants with M184V/I and HIV-1 RNA ≥ 50 cp/mL at their last visit, two had HIV-1 RNA < 100 cp/mL (one resuppressed on commercial B/F/TAF and one on ATV/RTV + F/TDF), and one had HIV-1 RNA 2,860 cp/mL, documented poor adherence, undetectable BIC plasma concentrations, and no treatment-emergent resistance
BL, baseline; OLE, open-label extension
Andreatta K, et al. EACS 2021. Poster PE1/19

Pooled analysis: Studies 4030, 4580, 1844, 1878 and 4449

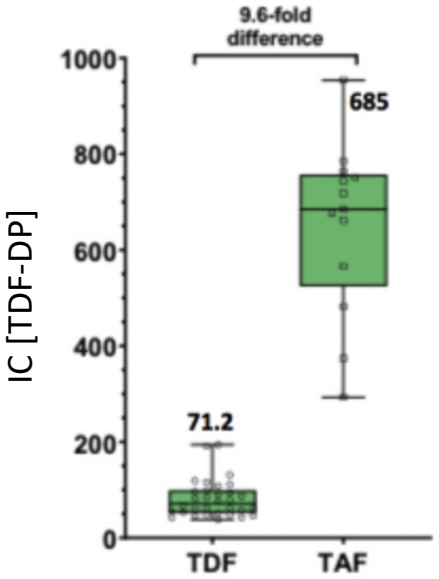
# Virologic Outcomes by Pre-existing TAMs: Last On-treatment Study Visit




**High rates of virologic suppression were maintained through 72 weeks after switching to B/F/TAF, regardless of pre-existing TAMs**

*No participants with ≥ 1 TAM and primary INSTI-R received B/F/TAF
R, resistance; TAM, thymidine analog mutation
Andreatta K, et al. EACS 2021, Poster PE1/6

# Do higher TFV-DP IC concentrations contribute to a higher genetic barrier of a cART?




**Genetic barrier?**

- Virological failure in people with HIV can be associated with ARV resistance, narrowing future options
- Genetic barrier to resistance
  - Threshold of mutations required for clinically meaningful loss of drug susceptibility
  - Likelihood to fail cART with resistance mutations
- Also influenced by
  - Drug's structure
  - Inhibitory quotient
  - Therapeutic index
  - PK forgiveness

# Mr W

- 61 y.o. MSM
- VL<50, CD4 821
- HIV + since 2001
- TOC in 2011 on TDF/3TC/DRV/r
- AUG 2015 switched to TDF/FTC + DTG
- Baseline RT not available
- Serum creatinine 154 microM/L; eGFR 40 mL/min (was 67 six months ago and deteriorated)
- BP 145/95 mmHg

# Mr W

- Medical Hx: depression, hypertension, peripheral neuropathy, hypercholesterolemia, benign prostatic hyperplasia, osteopenia (BMD 7 and 2 years ago)
- Comeds: citalopram, amitryptiline, amlodipine, bisoprolol, tamsulosin, vitamin D
- Intolerant to statins (?), on rosuvastatin 5 mg OD
- Co-morbidity management?
- cART management?

# Over50 patient pathway

› Int J STD AIDS. 2012 Aug;23(8):546-52. doi: 10.1258/ijsa.2012.011412.

## A dedicated clinic for HIV-positive individuals over 50 years of age: a multidisciplinary experience

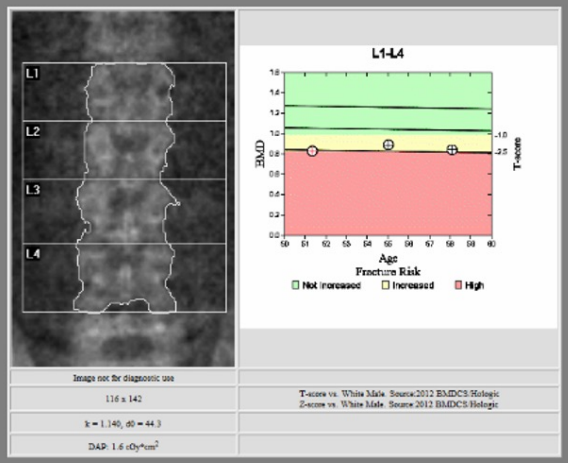
L Waters [1], B Patterson, A Scourfield, A Hughes, S de Silva, B Gazzard, S Barton, D Asboe, A Pozniak, M Boffito

› AIDS Res Hum Retroviruses. 2021 Aug 13. doi: 10.1089/AID.2021.0083. Online ahead of print.

## Evaluation of a Clinic Dedicated to People Aging with HIV at Chelsea and Westminster Hospital: Results of a 10-Year Experience

Branca Pereira [1 2], Maria Mazzitelli [1 3], Ana Milinkovic [1], Christina Casley [1], Javier Rubio [1], Rachel Channa [1], Nicolo Girometti [1], David Asboe [1], Anton Pozniak [1], Marta Boffito [1 2]

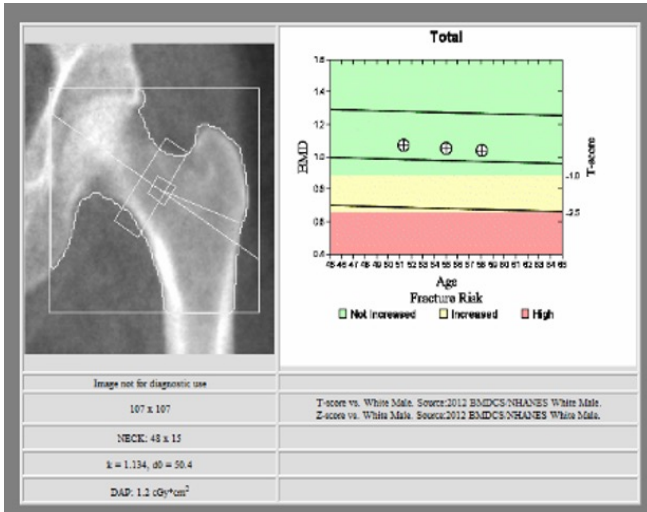
# BMD 2021




**Results Summary:**

| Region | Area[cm²] | BMC[(g)] | BMD[g/cm²] | T-score | PR (Peak Reference) | Z-score | AM (Age Matched) |
|---|---|---|---|---|---|---|---|
| L1 | 15.36 | 12.29 | 0.800 | -2.5 | 75 | -2.0 | 79 |
| L2 | 15.53 | 13.74 | 0.885 | -1.9 | 81 | -1.3 | 86 |
| L3 | 17.63 | 15.55 | 0.882 | -2.0 | 80 | -1.4 | 85 |
| L4 | 19.70 | 15.60 | 0.792 | -2.7 | 73 | -2.1 | 77 |
| **Total** | **68.22** | **57.19** | **0.838** | **-2.3** | 77 | **-1.7** | **81** |

Total BMD CV 1.0%, ACF = 1.032, BCF = 1.000, TH = 9.450




**Results Summary:**

| Region | Area[cm²] | BMC[(g)] | BMD[g/cm²] | T-score | PR (Peak Reference) | Z-score | AM (Age Matched) |
|---|---|---|---|---|---|---|---|
| **Neck** | **5.28** | **4.61** | **0.872** | **-0.4** | **94** | **0.5** | **108** |
| Total | 39.11 | 40.59 | 1.038 | 0.0 | 100 | 0.5 | 107 |

Total BMD CV 1.0%, ACF = 1.032, BCF = 1.000, TH = 6.533

## Renal assessment and CVD

- BP management
- uPCR

## Potential resistance - no access to information

- Switched to TAF/FTC/BIC STR

Continues statin, weight monitoring, lifestyle advice

# ART and Weight Gain: Take-Home Points

- New data help us understand how ART switches may result in weight gain
  - Switch data especially useful since it removes "return to health" phenomenon
- Switching off TDF – especially if combined with EFV – can lead to weight gain
  - 10% or more weight gain associated with TDF to TAF, EFV to either RPV or EVG/c
- Switching to DTG/3TC does not appear to lead to weight loss
  - Weight gain may occur with TDF/FTC/EFV to DTG/3TC switches
- Switching from DTG to BIC is weight-neutral
- The mechanism of these weight changes after switch remain unknown
  - KEY QUESTIONS: Do some regimens suppress weight? Or do some regimens cause increase weight? Or is it a combination of effects?
- Prospective clinical trials are investigating these issues further

ACCEPTED MANUSCRIPT

**Weight Change Following Antiretroviral Therapy Switch in People with Viral Suppression: Pooled Data from Randomized Clinical Trials**

Kristine M Erlandson ✉, Christoph C Carter, Kathleen Melbourne, Todd T Brown, Cal Cohen, Moupali Das, Stefan Esser, Hailin Huang, John R Koethe, Hal Martin, Grace A McComsey, Chloe Orkin, Frank A Post, Jürgen K Rockstroh, Paul E Sax, Hans-Jürgen Stellbrink, Laura Waters, Xuelian Wei, Jordan E Lake ✉

*Clinical Infectious Diseases*, ciab444, https://doi.org/10.1093/cid/ciab444

**Published:** 14 May 2021 **Article history** ▾

# Metabolic Clinic/ Live Well Pathway C&W

- To improve the health and well-being of PLWH
- HIV doctors specialising in metabolic health challenges, HIV dieticians and HIV physiotherapists
- Social-prescribing process could improve general quality of life, appropriate dietary regimens and physical exercise.

# What do we do?

**You can't prevent complications if you don't know they are there**

**Screening**

- Body composition – Weight, BMI, waist circumference
- BP and co-meds list
- Fasting Lipids
- Fasting Blood Sugar & HbA1c

**Annually and after ART start or switch**

# Kobler Metabolic Clinic/ Live Well Pathway C&W

**Criteria** well controlled HIV infection **+:**

- Diabetes mellitus(DM):HbA1c >55mmol/mol, poorly controlled DM
- Poorly controlled lipids
- Drug-drug interaction issues
- Nonalcoholic **fatty liver** disease/Non alcoholic **fatty liver** disease (NASH/NAFLD)
- Bone problems (osteopenia /osteoporosis)
- Difficulty maintaining healthy lifestyle and/or obesity

# Mr J

- 53 years old, MSM
- HIV diagnosed 2002:
  - No opportunistic infections
  - ARV treatment since 2003 (currently on TDF/FTC+EFV)

**PMH**:

- Hypertension, hyperlipidaemia, non alcoholic fatty liver disease, gynecomastia, osteoporosis
- Ex-smoker, 40 pack years; ETOH: 10-14 units per week
- QRISK 3- 22.1%; Q Diabetes: 85.7%
- BMI: 35 kg/**m**$^2$

- Co-medication:
  - Atorvastatin, ramipril, amlodipine

MSM, men-who-have-sex-with-men; PMH, past medical history
Fictional patient for illustration purposes only

# Mr J

- 53 years old, MSM
- HIV diagnosed 2002:
  - No opportunistic infections
  - ARV treatment since 2003 (currently on TDF/FTC+EFV)

Modernization of cART plus lifestyle interventions is today probably the best tool to optimize cART

MSM, men-who-have-sex-with-men; PMH, past medical history
Fictional patient for illustration purposes only

# Conclusions

- TAF is a modern ARV
- Component of well tolerated and high generic barrier cART
- Metabolic side effects still need investigation and are manageable mostly by lifestyle interventions
- Long term efficacy and tolerability data available