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2DR Debate: Should the Majority of People Living with HIV Be on a Two-Drug Regimen?

"Pro Standpoint"

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Conflict of Interest: JKR

- **Honoraria for lectures and/or consultancies from Abivax, Galapagos, Gilead, Janssen, MSD, NPO Petrovax Pharm LLC, Theratechnologies and ViiV.**

- **Research grants from Dt. Leberstiftung, DFG, DZIF, Hectorstiftung, NEAT ID.**

Who do you trust ???

What does Dr Waters think of 2DR therapy???

Review > Curr Opin Infect Dis. 2020 Feb;33(1):28-33. doi: 10.1097/QCO.0000000000000615.

Two drugs regimens for HIV

Laura Waters [1], Hannah Church [2]

Affiliations + expand

PMID: 31834030 DOI: 10.1097/QCO.0000000000000615

Abstract

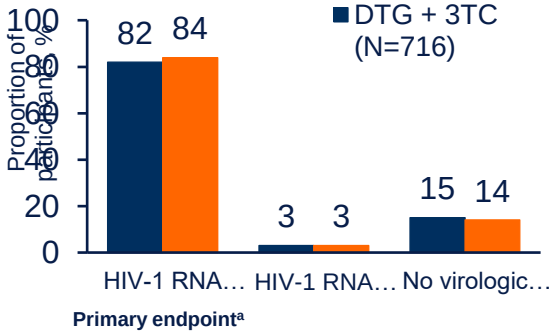
Purpose of review: As the evidence for two-drug regimens (2DR) for HIV treatment accumulates and 2DR start to enter consensus guidelines, this review covers the history, rationale and current evidence for 2DR in first-line and switch settings.

Recent findings: Until recently, most evidence for 2DR was for boosted protease inhibitor-based therapies but now we have large, randomized trials to support the use of dolutegravir (DTG)-based 2DR, both for initial therapy and suppressed switch, with high efficacy and no emergent resistance at failure.

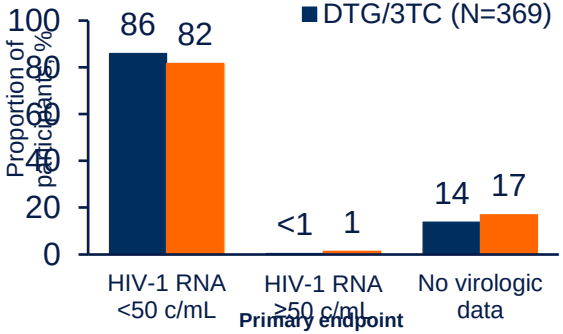
DTG/3TC Has Demonstrated Non-Inferior Efficacy Versus Other ART Regimens in Treatment-Naive and Treatment-Experienced PLWH

- Rapid treatment of HIV-1 infection has been associated with improved linkage to and retention in care and reduced time to virologic suppression in PLWH[1,2]
- DTG/3TC has demonstrated non-inferior efficacy, a good safety profile, and a high barrier to resistance in treatment-naive PLWH in the GEMINI studies (vs DTG + TDF/FTC)[3-5] and treatment-experienced, virologically suppressed PLWH in the TANGO (vs continuing 3- or 4-drug TAF-based regimens)[6-8] and SALSA studies (vs continuing any current 3- or 4-drug ART regimen)[9]

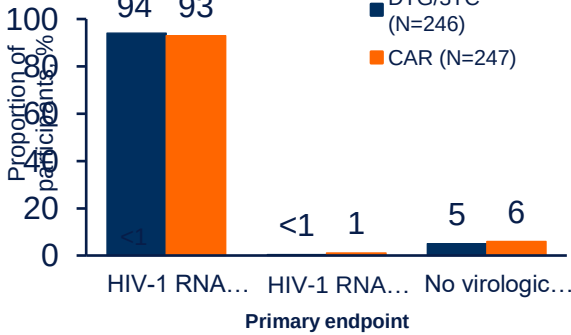
GEMINI-1 and GEMINI-2, Week 144
Virologic Outcomes (Snapshot)[5]



TANGO, Week 144
Virologic Outcomes (Snapshot)[8]



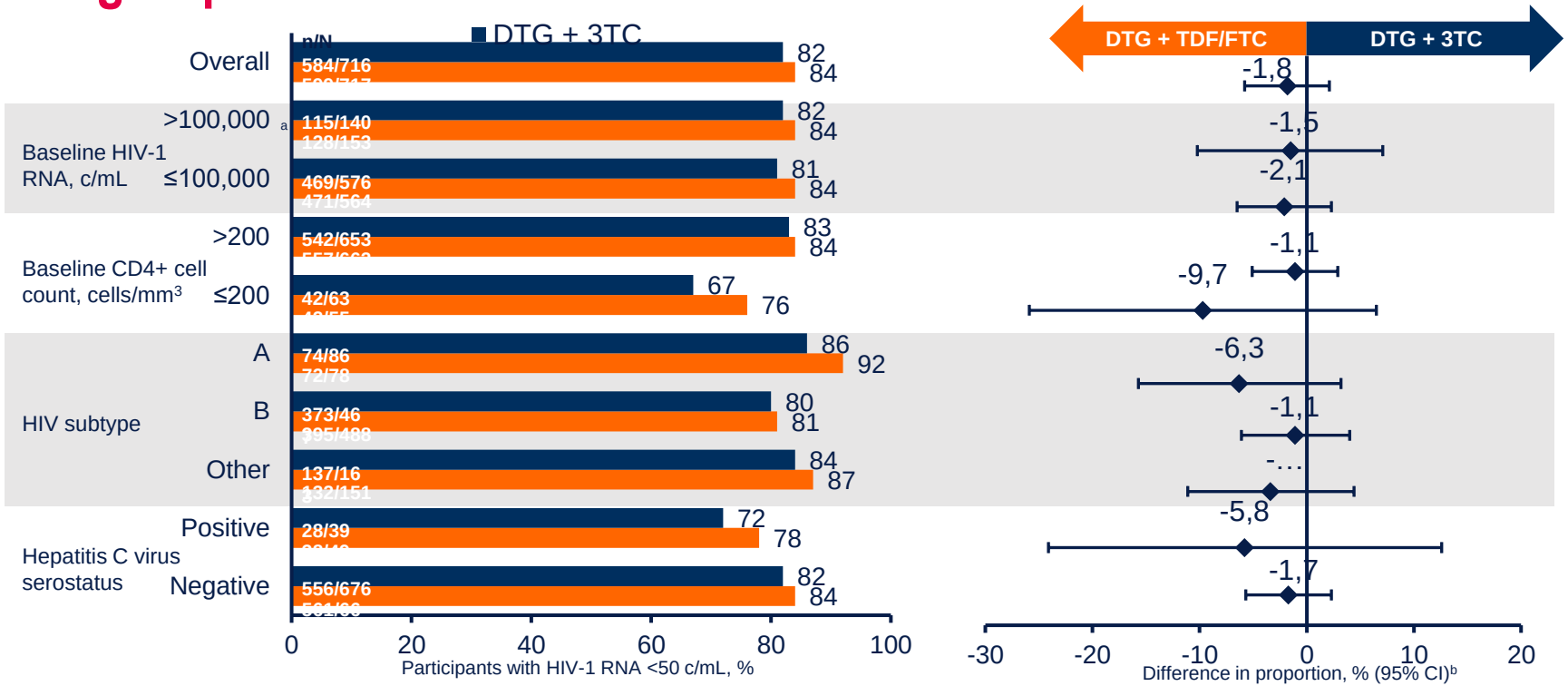
SALSA, Week 48
Virologic Outcomes (Snapshot)[9]



[a]For participants with baseline HIV-1 RNA >500,000 c/mL: DTG + 3TC, 10/13 (77%); DTG + TDF/FTC, 12/15 (80%).[10]

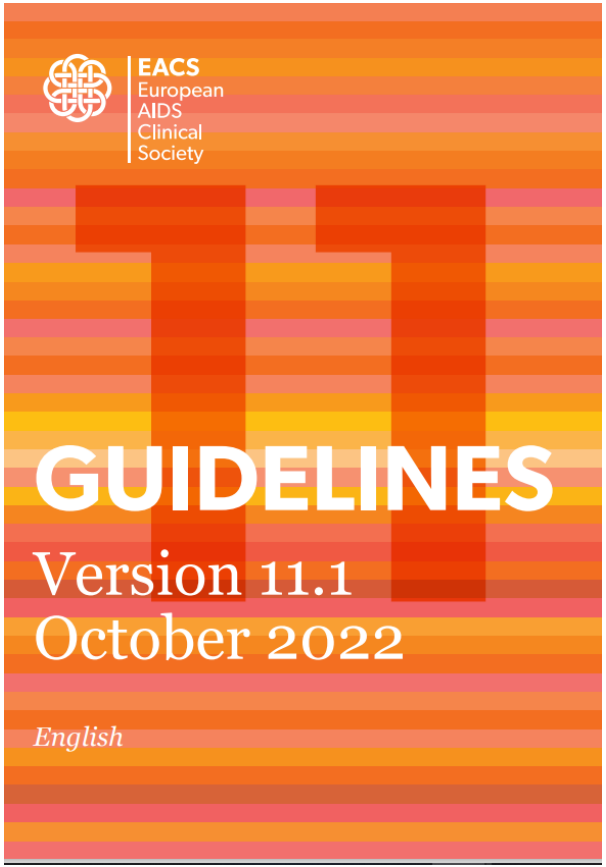
1. CDC. Understanding the HIV Care Continuum. 2019. **2.** DHHS. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf. Accessed August 12, 2021. **3.** Cahn et al. *Lancet*. 2019;393:143-155. **4.** Cahn et al. *J Acquir Immune Defic Syndr*. 2020;83:310-318. **5.** Cahn et al. HIV Glasgow 2020; Virtual. Poster P018. **6.** van Wyk et al. *Clin Infect Dis*. 2020;71:1920-1929. **7.** van Wyk et al. HIV Glasgow 2020; Virtual. Slides O441. **8.** van Wyk et al. IAS 2021; Virtual. Poster PEB164. **9.** Llibre et al. IAS 2021; Virtual. Slides OALB0303. **10.** Orkin et al. CROI 2021; Virtual. Science spotlight 1991.

HIV-1 RNA <50 c/mL Was Comparable Across Baseline Disease Subgroups at Week 144



[a]Includes values for HIV-1 RNA >250,000 c/mL (DTG + 3TC, 41/51 [80%]; DTG + TDF/FTC, 37/46 [80%]), HIV-1 RNA >400,000 c/mL (DTG + 3TC, 15/18 [83%]; DTG + TDF/FTC, 19/24 [79%]), and HIV-1 RNA >500,000 c/mL (DTG + 3TC, 10/13 [77%]; DTG + TDF/FTC, 12/15 [80%]). [b]Adjusted difference for overall population (DTG + 3TC − DTG + TDF/FTC). Unadjusted difference for subgroups calculated by proportion on DTG + 3TC − proportion on DTG + TDF/FTC.

EACS Guidelines version 11.1

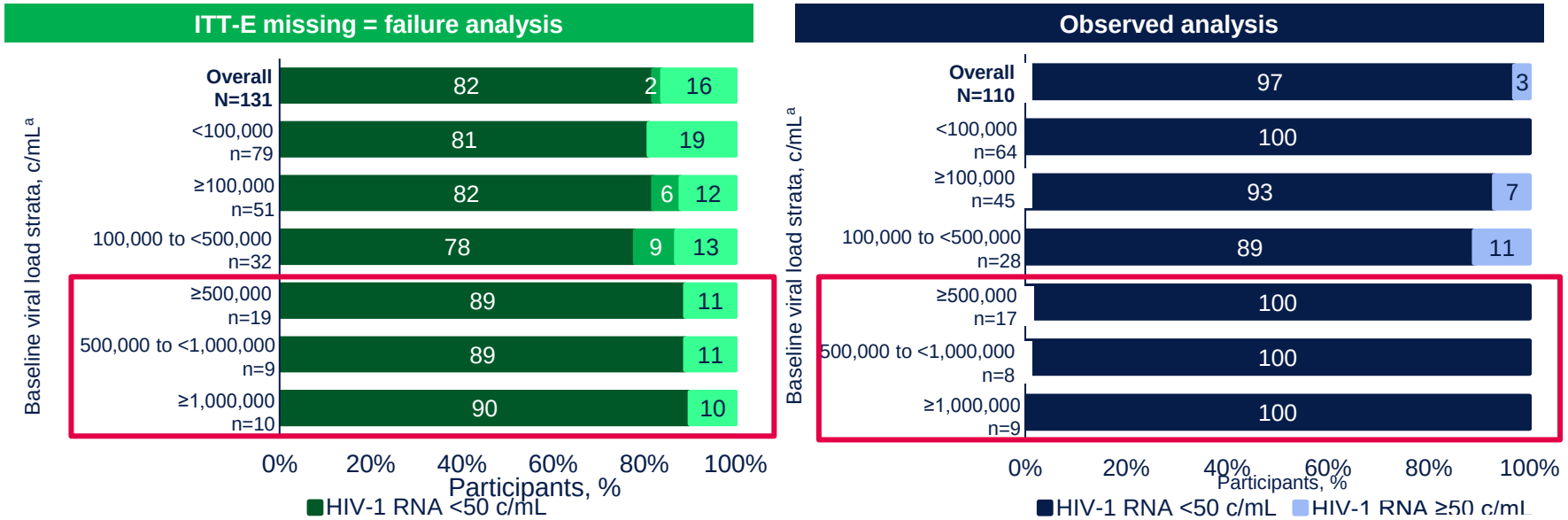


At EACS we do love footnotes……

ART is recommended in all adult PLWH, irrespective of CD4 counts[I]

Regimen	Main requirements	Additional guidance (see footnotes)
Recommended regimens		
2 NRTIs + INSTI		
ABC/3TC + DTG ABC/3TC/DTG	HLA-B*57:01 negative HBsAg negative	I (ABC: HLA-B*57:01, cardiovascular risk) II (Weight increase (DTG))
TAF/FTC/BIC		II (Weight increase (BIC, TAF))
TAF/FTC or TDF/XTC + DTG		II (Weight increase (DTG, TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing)
TAF/FTC or TDF/XTC + RAL qd or bid		II (Weight increase (RAL, TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) IV (RAL: dosing)
1 NRTI + INSTI		
XTC + DTG or 3TC/DTG	HBsAg negative HIV-VL < 500,000 copies/mL Not recommended after PrEP failure	II (Weight increase (DTG)) V (3TC/DTG not after PrEP failure)
2 NRTIs + NNRTI		
TAF/FTC or TDF/XTC + DOR or TDF/3TC/DOR		II (Weight increase (TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VI (DOR: caveats, HIV-2)
Alternative regimens		
2 NRTIs + NNRTI		
TAF/FTC or TDF/XTC + EFV or TDF/FTC/EFV	At bedtime or 2 hours before dinner	II (Weight increase (TAF) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VII (EFV: neuro-psychiatric adverse events. HIV-2 or HIV-1 group 0, dosing)
TAF/FTC or TDF/XTC + RPV or TAF/FTC/RPV or TDF/FTC/RPV	CD4 count > 200 cells/µL HIV-VL < 100,000 copies/mL Not on gastric pH increasing agents With food	II (Weight increase (TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VIII (RPV: HIV-2)
2 NRTIs + PI/r or PI/c		

At Week 48, Virologic Suppression Rates Were High in Participants With Baseline Viral Load ≥500,000 c/mL



- 11/19 participants with baseline HIV-1 RNA ≥500,000 c/mL had CD4+ cell count <200 cells/mm^3; 10 achieved HIV-1 RNA <50 c/mL at Week 48 and 1 withdrew at Week 4 due to physician decision
- Median (95% CI) time to suppression for participants with baseline viral load ≥500,000 c/mL was 60 (56-169) days

ITT-E missing = failure analysis: all participants in the ITT-E population, regardless of ART regimen; observed analysis: all participants with available HIV-1 RNA data, regardless of ART regimen.
[a]1 (<1%) participant had missing plasma HIV-1 RNA results at baseline.

Among Participants With CVF or Baseline HBV Co-infection, No Evidence of Treatment-Emergent Resistance Was Observed

	Participants meeting CVF criteria at Week 48	Number of HIV resistance-associated mutations detected
Total population	2	0
Participants with baseline HIV-1 RNA ≥500,000 c/mL	1	0

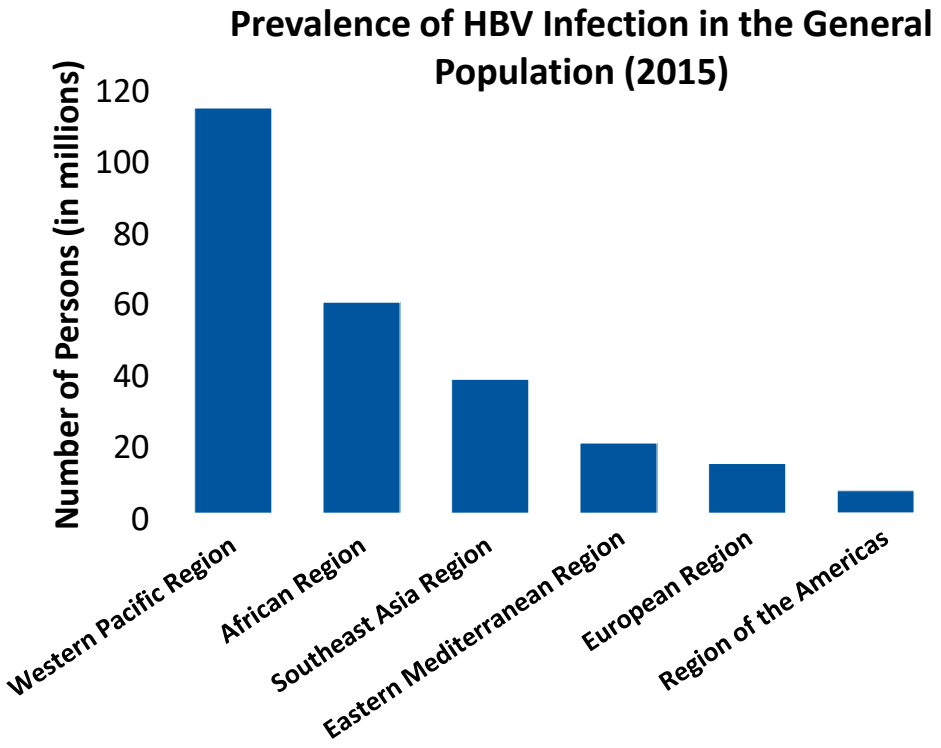
- Both participants meeting CVF criteria remained on DTG/3TC in study (1 participant suppressed to HIV-1 RNA <50 c/mL and 1 participant had HIV-1 RNA 70 c/mL at Week 48)
  - The participant with high baseline viral load (13,987,640 c/mL) was not suppressed at Week 24; HIV-1 RNA was 220 c/mL at Week 36 (CVF criteria met) and 63 c/mL at Week 48 followed by a retest at 48 c/mL

	Participants with baseline HBV co-infection	Number of HBV resistance-associated mutations detected
Total population	7	0
Participants with successful resistance tests	3	0

Rolle et al. IAS 2021; Virtual. Poster PEB182.

Global Status of HBV Infection

- In 2019: 296 million people living with chronic HBV infection; majority in African and Western Pacific regions
- 7.4% of persons with HIV also have HBV coinfection (2.7 million persons)
- The global target of hepatitis B surface antigen prevalence of below 1% for 2020 among children younger than five years is one of the first 2020 targets of the health-related Sustainable Development Goals to be met.



The Lack of Effect of Prior M184V on Treatment Outcomes is Also Apparent in the Real-world Setting

			M184V					
Cohort	**Study type**	**Patients on DTG + 3TC, N**	**Patients with M184V/I, n**	**M184V detection method, n**	**Time point**	**Patients maintaining/achieving virologic effectiveness (<50 c/mL), n or % or probability of VF**	**Patients with VF and M184V, n/N**	**VF definition**
SOLAR 3D[1] (United States)	Prospective, open-label	100	**50**	Historical genotype	Week 48	92% (46/50) maintained	**0/50**	VL ≥50 c/mL followed by VL >200 c/mL
Dat'AIDS[2] (France)	Multicentre, retrospective	695	**105**	NR	NA	No significant difference in the probability of VF between M184V+ and M184V– groups after a median follow up of 1.2 years (p=0.81)	**2/105**	Confirmed VL >50c/mL, or a single VL ≥200 c/mL
ODACRE[3] (Italy)	Multicentre, observational, retrospective	556	**45**	NR	Week 144	NR for patients with M184V Overall population: 96.5% estimated probability of maintaining virologic suppression	**2/45**	Confirmed VL ≥50 c/mL, or a single VL ≥1,000 c/mL
LAMRES[4] (Europe)	Multicentre, observational, retrospective	533	**37**	Historical RNA, 29 Historical DNA, 7 Historical RNA and DNA, 1	1 year, 2 years	Probability of VF with presence vs absence of M184V: 5.4% vs 2.6% at 1 year; 9.2% vs 4.4% at 2 years (p=0.345) Higher probability of VF if M184V detected ≤5 years vs >5 years before switching to DTG + 3TC	**3/37**	Confirmed VL >50 c/mL, or a single VL ≥200 c/mL
ARCA[5] (Italy)	Observational, retrospective	126	**21**	Historical RNA	1 year	Overall population: 95.1% and 96.2% estimated probability of remaining free from VF in M184V+ (n=349) and M184V- (n=87) patients treated with 3TC + (bPI or RAL) 2DR	**0 (2 VFs in M184V-negative group)**	Confirmed VL >50 c/mL, or a single VL ≥200 c/mL
DOLULAM[6,7] (France)	Monocentric, observational, prospective	27	**17**	Historical RNA, 8 Sanger DNA, 2 NGS, 7	2 years	17 (100%) patients remained free from VF (1 patient experienced a blip)	**0/17**	Confirmed VL >50 c/mL
DOLAMA[8] (Spain)	Multicentre, observational, retrospective	177	**4 (of 90 tested)**	BL genotypic test	Week 48	75% (3/4) patients remained free of VF	**1/4**	Confirmed VL >50 c/mL

Results indicate that the presence of M184V at BL in virologically suppressed patients does not affect the virologic effectiveness of DTG + 3TC in clinical practice

Potential overlap between patient cohorts cannot be ruled out
bPI, boosted protease inhibitor; **ISS, i**nvestigator-sponsored studies; **NGS,** next-generation sequencing

1. Blick G, et al. EACS 2021. Poster PE2-65; **2.** Hocqueloux L, et al. EACS 2021. Poster OS1-2
3. Baldin G, et al. Int J Antimicrob Agents 2019;54:728–34; **4.** Santoro M, et al. CROI 2021; Abstract P429
5. Gagliardini R, et al. Open Forum Infect Dis 2018; 5(6):ofy113; **6.** Charpentier C, et al. J Antimicrob Chemother 2017;72:2831–6
7. Reynes J, et al. IAS 2017; MOPEB0322; **8.** Hidalgo-Tenorio C, et al. Medicine 2019;98:e16813

TAF really that s

Heron *et al. BMC Nephrology* (2020) 21:339
https://doi.org/10.1186/s12882-020-01981-9

CASE REPORT

Renal proximal tubul
infected patient treat
alafenamide and gen

Jack E. Heron[1*], Mark Bloch[2,3], Vinay Vanguru[4], John Saunders[1] and David

Abstract

Background: The nucleotide reverse transcriptase inhibitor Tenofovir Alafena
tenofovir (TFV) and possesses a superior renal safety profile compared with te
to unique pharmacokinetic characteristics, treatment with TAF is not associate
tubular accumulation of TFV. TAF is associated with a lower risk of acute kidn
proteinuria and renal proximal tubular dysfunction than treatment with TDF.
been reported in clinical trials of TAF. It is unknown whether treatment with
in proximal tubular cells and cause nephrotoxicity under certain clinical circu

Case presentation: Here we report the case of a patient on stable TAF-base
infection who developed proximal tubulopathy when treated with gentamici
context of relapsed Hodgkin lymphoma. Eighteen days after commencing ch
lymphoma the patient presented to hospital with fevers, hypotension and ne
commenced on piperacillin, tazobactam and gentamicin. Within 24 h the pat
and hypophosphataemia requiring intravenous replacement therapy. There w

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https://doi.org/10.1

CASE REP

Tenofo
report

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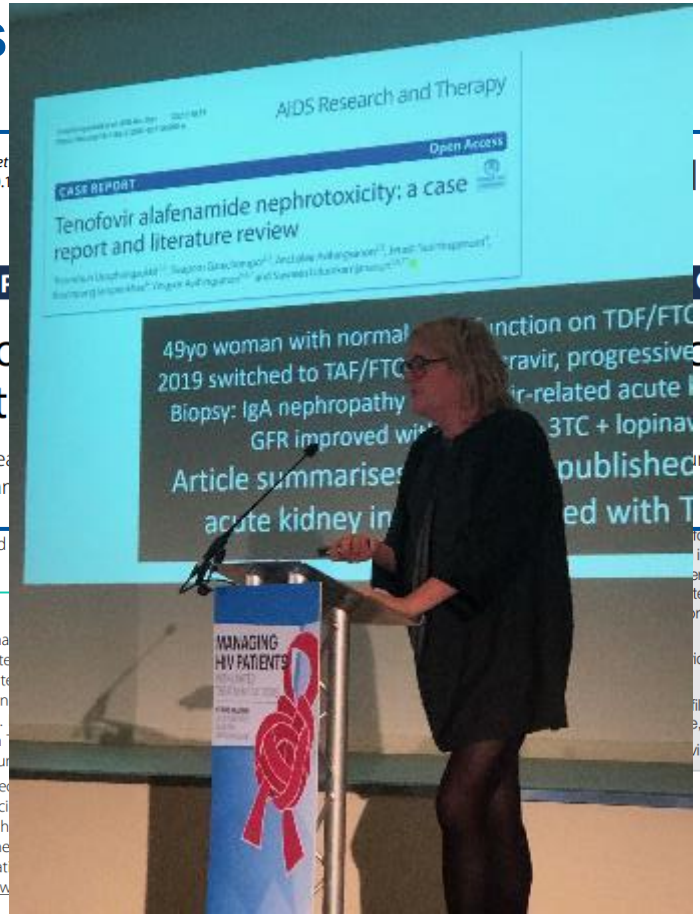


l Therapy

Open Access

case

Check for updates

rintrspanont[4],

Medicine

OPEN

city in an

aithin A. McMahon, MD, PhD[a],

reverse transcriptase inhibitor. TAF is less
ovir disoproxil fumarate (TDF). Tenofovir causes mitochondrial dysfunction and
in proximal tubule cells. TAF's unique pharmacokinetic profile enables provision of
er concentrations reach renal tubules minimizing intracellular accumulation and
ted with the histologic markers of tenofovir-associated nephrotoxicity that are seen
roximal tubule cells. Here, we report a patient with dysmorphic mitochondria on

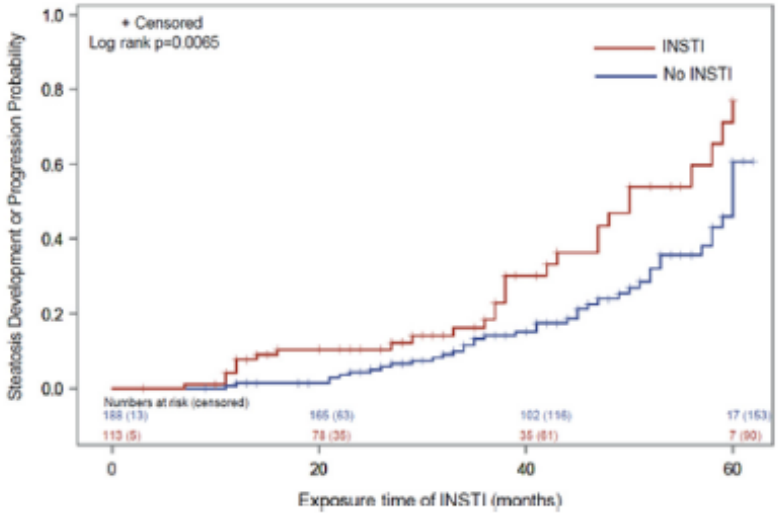
iduals may experience tubular mitochondrial injury from lower concentrations of

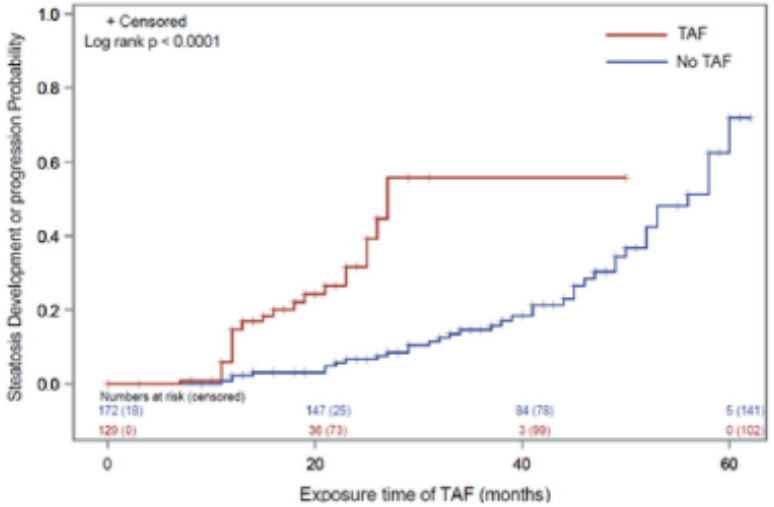
iltration rate, HCV = hepatitis C virus, HIV = human immunodeficiency virus, PTC =
e, TDF = tenofovir disoproxil fumarate, TFV = tenofovir.

ir alafenamide, tenofovir nephrotoxicity

Specific ART as risk factor for steatosis progression

- N=301 mono-infected patients with serial Fibroscan with CAP, followed for a mean 41.8±14.8 months
- Progression of hepatic steatosis defined as development of CAP>238 dB/m or progression of steatosis to grade 2 (CAP>260) or 3 (CAP>292) during follow-up





Bischoff, eClinicalMed 2021

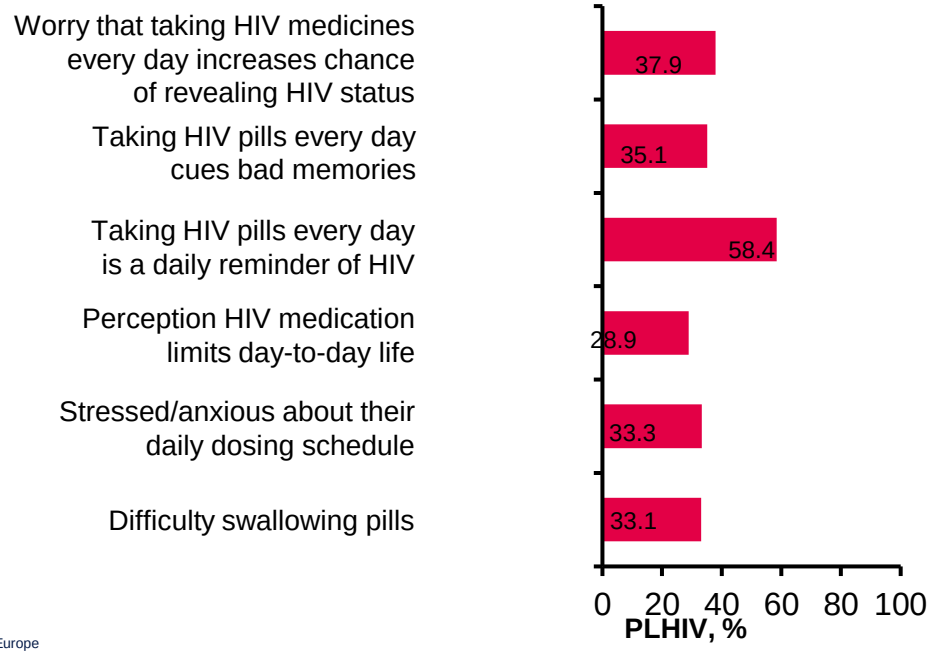
Cost reduction with 2DR in Germany

- **Descovy 30 Tablets = 516,77 Euro**
- **Tivicay 30 tablets = 725,63 Euro**
- **Descovy + Tivicay = 1242,40 Euro**
- **Biktarvy 30 Tablets = 924,75 Euro**
- **Dovato 30 Tablets = 857, 55 Euro**

Increased flexibility of ART delivery is needed to meet the diverse needs of PLHIV

- PLHIV continue to face physical, emotional, and psychosocial challenges with daily oral ART[1]
- These challenges have been associated with poor health outcomes including low treatment satisfaction, self-reported virologic failure, suboptimal self-rated overall health, and poor adherence[1,2]

Percentage of PLHIV who reported challenges with their treatment*[1]



*The Positive Perspectives Study 2019 was conducted across 25 countries (N=2,389). Participants were enrolled from Europe (n=1,119), North America (n=520), South Africa (n=179), Australia (n=120), Japan (n=75), Mexico (n=63), Brazil (n=58), Taiwan (n=55), Argentina (n=50), Chile (n=50), China (n=50), and South Korea (n=50)[2]

ART, antiretroviral therapy

1. de los Rios P, et al. AIDS Behav 2020 [Epub ahead of print]
2. de los Rios P, et al. Prev Med 2020 [Epub ahead of print]

And what about the body language?

Summary

- 2 DR (DOL/3TC) equally efficacious and no resistance development in first-line or switch therapy (says Dr Waters)
- Less drugs promise less short and long-term toxicity
- TAF containing 3DR therapy is associated with more weight gain
- Cost savings possible with less drugs…….
- Pills size becomes smaller with less drugs……
- 2DR therapy also available with different mode of delivery addressing patient needs and improving quality of life

» **2DR is the ideal antiretroviral treatment option for the majority of PLWH**

Laura after the debate