HIV virologic failure:
Selected topics & new evidence in the integrase inhibitor era

Richard A. Murphy, MD, MPH

Chief, Inf. Diseases, White River Junction Veterans Affairs Medical Center

Associate Professor of Medicine, Geisel School of Medicine at Dartmouth

Learning objectives

- To describe causes of virologic failure (VF) in patients receiving TLD
- To provide an update on drug resistance in patients receiving TLD2 who experience VF
- To highlight that VF frequently occurs in patients with advanced HIV and provide recommendations

Definitions

- TLD1: Patient on DTG-based regimen with no prior virologic failure

- TLD2: Patient on DTG-based regimen after failing a prior regimen

    - *Sensible to include those switched to TLD from EFV or NVP ART **when viremic***

Organization	Definition
WHO	Viral load >1000 c/mL based on 2 VLs at least 3 months apart, with EAC following first VL
South Africa	Equivalent

2023 WHO Policy Brief: The Role of Virologic Suppression

POLL

After starting TLD1, when can we expect most patients with BL VL <100,000 c/ul to reach an undetectable VL?

1. 2 months
2. 6 months
3. 9 months
4. 12 months

How large a problem is VL >1000 c/ul in patients receiving TLD1?

Patients starting ART 2019-22 in Ethekwini

Pts in routine care who started DTG or EFV-based ART 2019-22:

At 12m, 89% (12911/14515) retained + VL obtained

82% suppressed <50 c/mL

18% not virologically suppressed

Dorwad et al. Lancet HIV 2023

Approximately 5% on TLD have VL>1000 after starting 12 months prior

Regimen	Viral load at 12 months		
	<50	50-999	>=1000
Non-DTG regimen	81.4% (5327)	10.1% (663)	8.4% (551)
DTG regimen	83.0% (5289)	11.6% (740)	5.4% (341)
Total	82.2% (10616)	10.9% (1403)	6.9% (892)

Additional data courtesy of Dr Jienchi Dorward from Dorwad et al. Lancet HIV 2023

Case

- 45 yo F with HIV diagnosed 5 y ago
  - CD4 456, no OI. Reports no prior ART
- 2 y ago developed TB lymphadenitis. Began RIPE then TLD without addit. DTG
  - She achieved UD VL and TB cured.
  - However 6 m ago she had a VL of 2345 c/ml and referred for adh. support
  - Today viral load is 3340 c/ml, CD4 345 and she mentions occasional diarrhea for 1 m.

POLL

Which of these is the most likely cause for current VL > 1000 c?

1. DTG resistance
2. Additional DTG 50 mg/day was not given
3. Poor ART absorption
4. Inadequate adherence

Management of VF on TLD in South Africa

Regimen	Definition	Resistance testing	Regimen change
TLD-1	2 VL ≥1000 c/mL	Not recommended	Not recommended* ABCDE & VL in 6m
TLD-2 < 2 years	2 VL ≥1000 c/mL	Not recommended	Not recommended* ABCDE & VL in 6m
TLD-2 > 2 years	2 VL ≥1000 c/mL	Consider in discussion with HIV expert	→ Individualized regimen*

* If CD4 <200 at virologic failure, discuss with HIV expert

South Africa ART Guidelines 2023

Approach to virologic failure

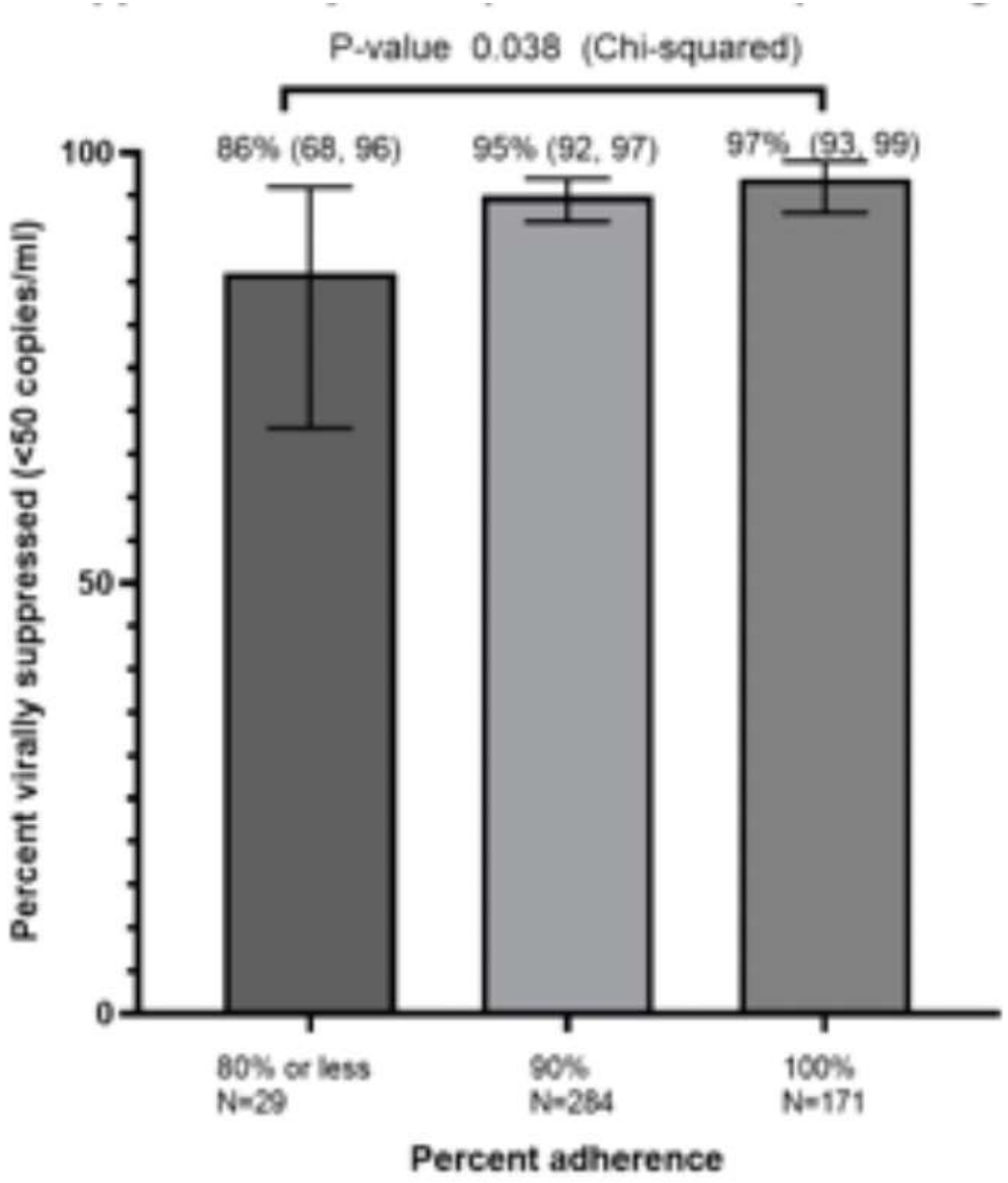
- Inadequate adherence
  - Begin to assess w/ self-report, pharmacy refills, missed visits
- Drug resistance

- Consider drug-drug interactions
- Recent illness or vaccinations?
- Poor absorption?

What adherence needed for virologic suppression on TLD?

- Traditionally we told patents 95% adherence needed for suppression
  - These estimates were based on older studies with unboosted PIs
- For TLD, useful to know the level of adherence needed for suppression
  - Some may not be capable of 100% adherence but still can suppress
- In this study they related self-reported adherence and viral suppression on TLD

Catalano et al Public Health Theses (Yale), 2022



80% **90%** **100%**

Established risk factors for low ART adherence

- **Youth**
- **Male gender**
- **Prior poor adherence**

- Adverse events
  - Tends to occur in those with *higher adherence* but can lead to discontinuation
- Markers of low SES
  - Unemployment, less than secondary education, experiencing homelessness
- Active alcohol / substance use disorder
- Poorly controlled mental illness

Sharing ART is also a occurring and a form of inadequate adherence

- In Uganda study, ART diversion defined as giving, receiving, buying or selling
- Buying and selling was uncommon but giving / receiving ART was freq.
  - Most common in young men 25-34 years (almost 20%)
  - Less common in women and older groups

- Giving ART linked with 2X risk of VF
  - 17% who gave ART to others viremic

ART diversion	Viremic/Total (%)	PR[a] (95% CI)	p-value
No diversion	209/2469 (8.5)	Ref	-
Gave only	10/58 (17.2)	2·04 (1·14-3·63)	0·016
Received only	2/49 (4.1)	0·48 (0·12-1·89)	0·294
Gave and received	10/131 (7.6)	0·90 (0·49-1·66)	0·740
Bought	3/18 (16.7)	1·97 (0·70-5·58)	0·202

Kennedy et al CROI 2023 OA-13

New insights: nonadherence is…..

~30% → UNINTENTIONAL vs INTENTIONAL ← Up to 70%

- FORGETTING
- SHIFT WORK
- COST/ACCESS
- CONFUSION
- WORK RESTRICTIONS

- MISTRUST
- FEAR OF SIDE EFFECTS
- MENTAL ILLNESS
- LACK OF BELIEF IN BENEFIT
- FEAR OF DEPENDENCY
- FEAR IT IS DANGEROUS
- LACK OF DESIRE
- NO APPARENT BENEFIT
- ALTRUISM

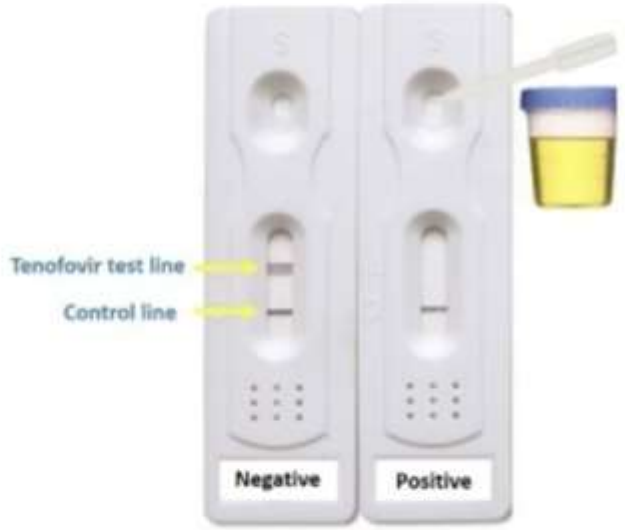
PrEP trials, 90%+ pill count, 30-50% plasma drug testing

- Amico R. JAIDS. 2014. Van Damme NEJM 2012. van der Straten J Int AIDS Soc. 2016

Coming to a clinic near you ?

Abbott/OraSure POC urine TFV

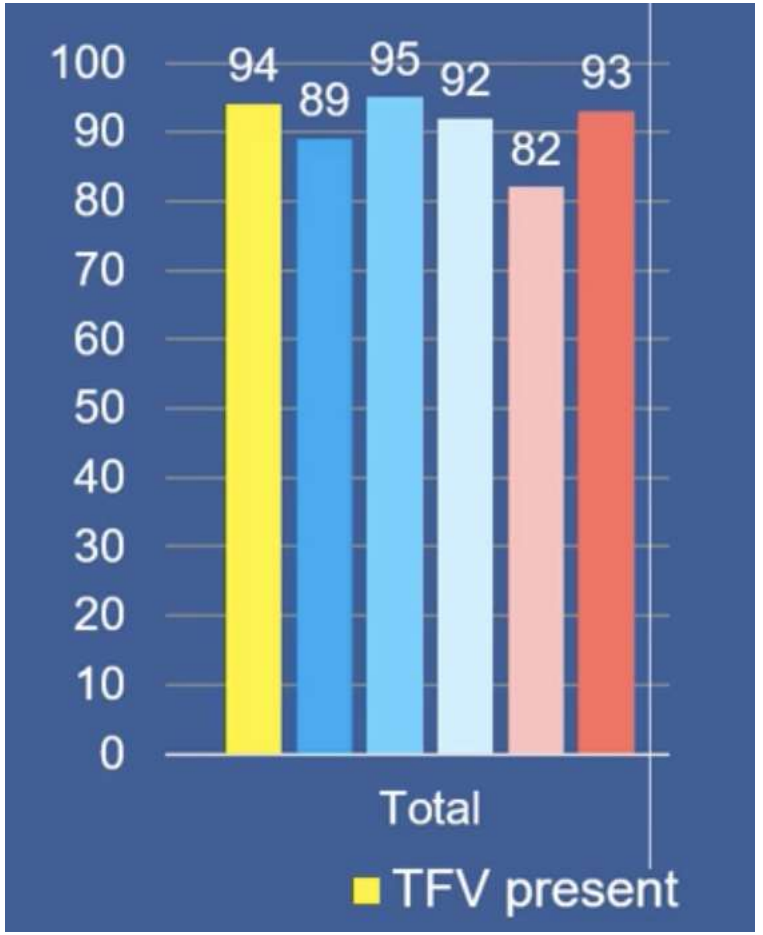
- Available 2024?
- Results 5-10 minutes, recent dose TAF and TDF
- Correlations with outcomes
- Patient counseling/white coat dosing?



Peter Anderson, CROI 2023

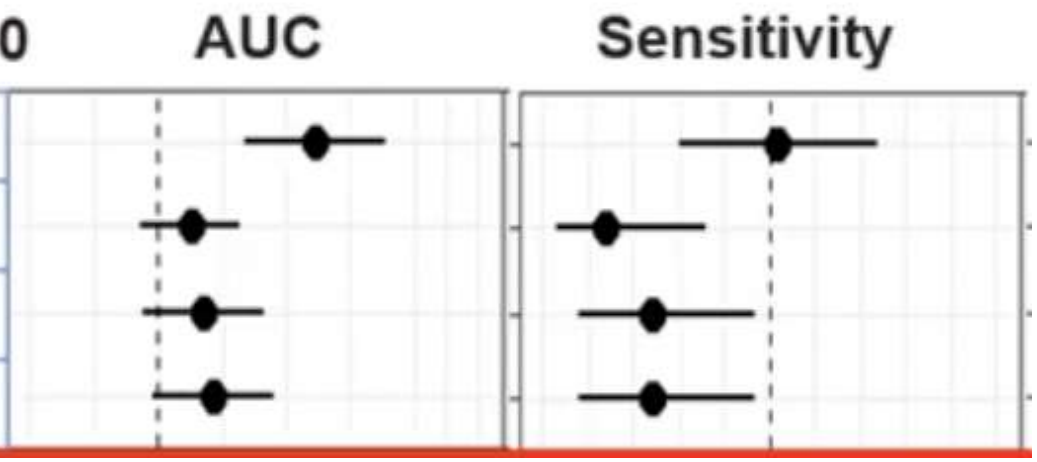
How does urine tenofovir testing look in routine ART care in S. Africa?

- In Gugulethu, those presenting for routine VL enrolled → Abbott urine TDF
  - Self-report also collected
- TDF test has 2 possible results: (+) or (-)



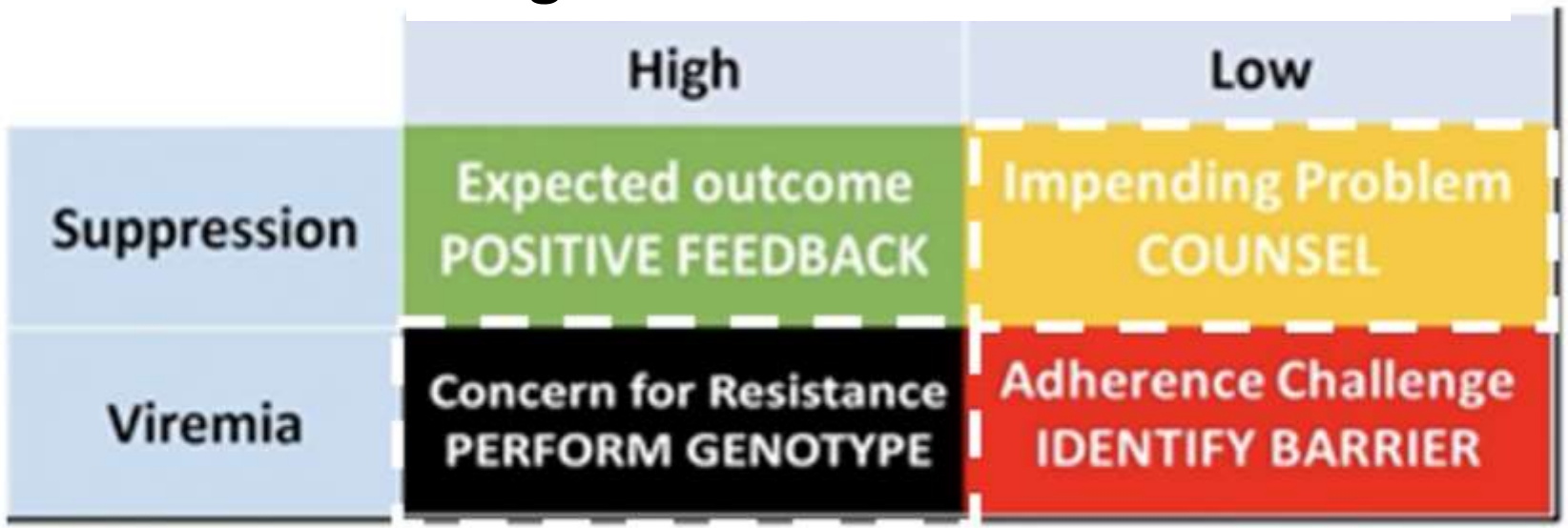
TFV present | No doses missed - 7d | <2 doses missed 7d | No doses missed 3d | VL <50 copies/mL | VL <1000 copies/mL

		≥1000	<1000
All participants n=314	Urine LFA, TFV absent	11	9
	Missed ≥2 doses, 7d	3	12
	Missed ≥1 doses, 7d	5	28
	Missed ≥1 doses, 3d	5	19



How might this work in the clinic?

Drug concentration in urine or blood



Predicting future viremia…
Grinsteiner 2023 ARHR
Jennings 2022 AIDS
Odayar 2022 CID
Morrow 2019 JID

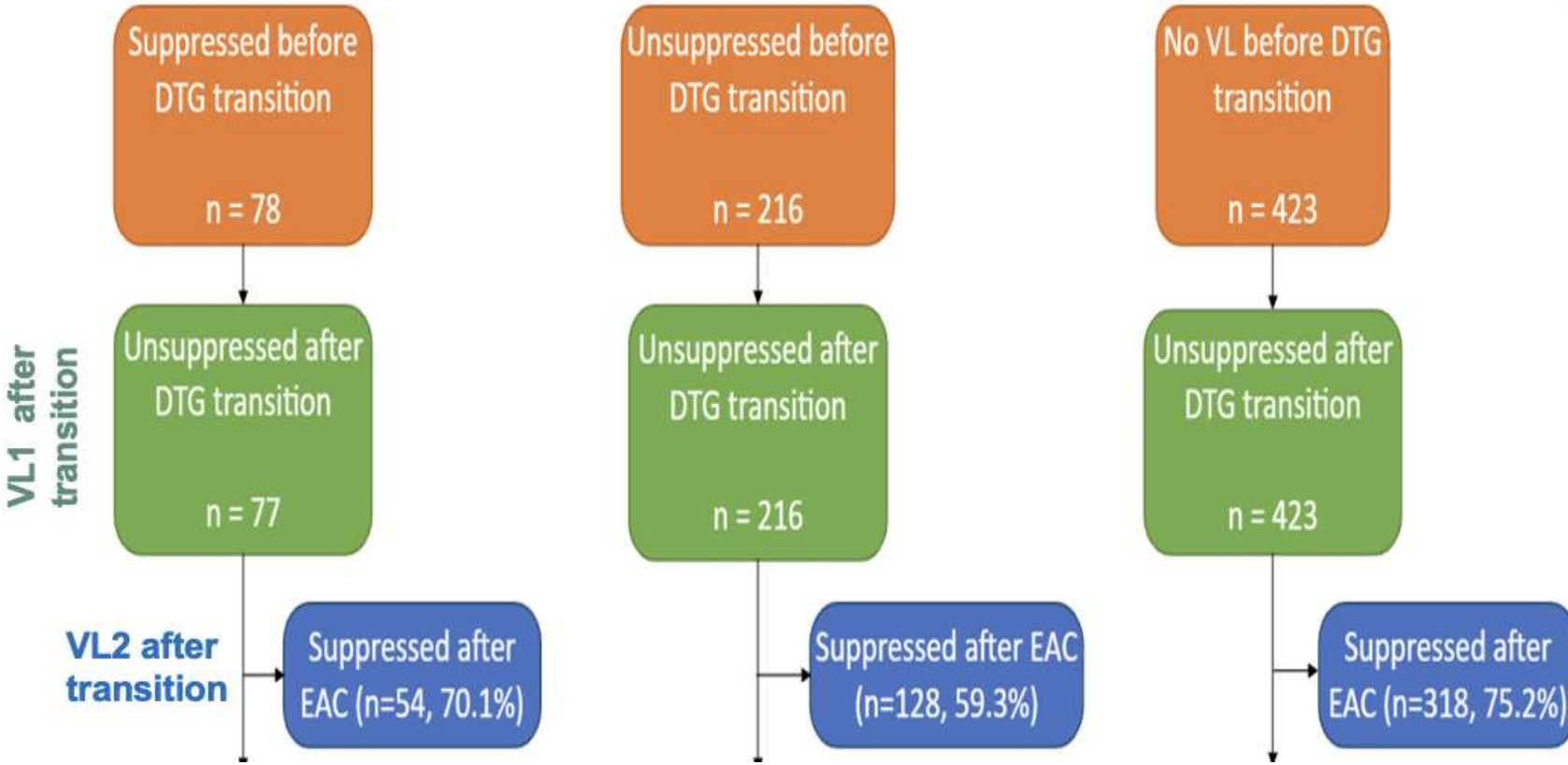
Predicting virologic resistance…
Castillo-Mancilla 2021 J Int AIDS Soc
Yager 2019 J Int Assoc Provid
Yan PLoS One 2016
Van Zyl JAIDS 2011
Abstract 205 CROI 2023

Kristofich M. 2021. Ther Adv Infectious Dis. Spinelli M. Current HIV/AIDS Reports (2020).

Slide: Peter Anderson, CROI 2023

Mozambique (1/2): 7 health care facilities
Will pts on TLD with VL >1000 resuppress after EAC?

- Enrolled adults (N=716) on TLD with recent VL >1000 who completed 3 EAC visits
- All transitioned to TLD from prior ART, most often EFV/FTC/TDF (79%)
- At repeat VL, 30% had 2nd VL>1000, while 70% suppressed VL



Bhatt et al AIDS Conference 2023

ADVANCE: Most patients randomized to TLD1 but had viremia resuppressed subsequently

- Patients starting DTG-based ART had wk 48 VL
- Participants not switched after a single VL >1000 → received EAC
- ~75% on DTG later had VL<50 subsequently <u>without</u> switch

Baseline viral load	Week 48 viral load	Follow-up VL
33 276	30 949	<50 in window
21 423	7201	<50 week 84
20 048	3067	<50 week 96
39130	332	<50 week 96
41 774	66	<50 week 96
252	219	<50 week 96
111 443	2203	<50 week 96
39 449	91	<50 week 96
11 599	41 588	<50 week 72
10 612	3926	<50 week 72
13 474	50	<50 week 60
107 696	42 606	16 545 at week 96
206 058	1110	4822 at week 96
4130	448	677 at week 96
12 317	6358	104 at week 96
93 742	72	52 at week 84
185 339	397 926	42 295 at week 72

This was NOT the case in the TEE arm: only ~40% later suppressed

Pepperell et al. 2020 AIDS

Talking about adherence

1. Avoid punitive approach
   - Avoid cycle where visits focus on “failure;” research shows after VF incr. risk of LTFU
   - Although it tops your agenda, HIV may not be most pressing problem patient facing

2. I try to be genuinely ”present” when discussing barriers with patients
   - Allow space to open for discussion of difficult barriers that can be hard to discuss

3. Touch on key causes of low adherence…2023 SA Guidelines useful
   - **Mistaken beliefs and fears (e.g. low belief in necessity of ART)**
   - Patient who travels for extended periods of time
   - Depression and other mental illness that is not controlled
   - Alcohol or substance disorders
   - Stigma / non-disclosure
   - Side effects

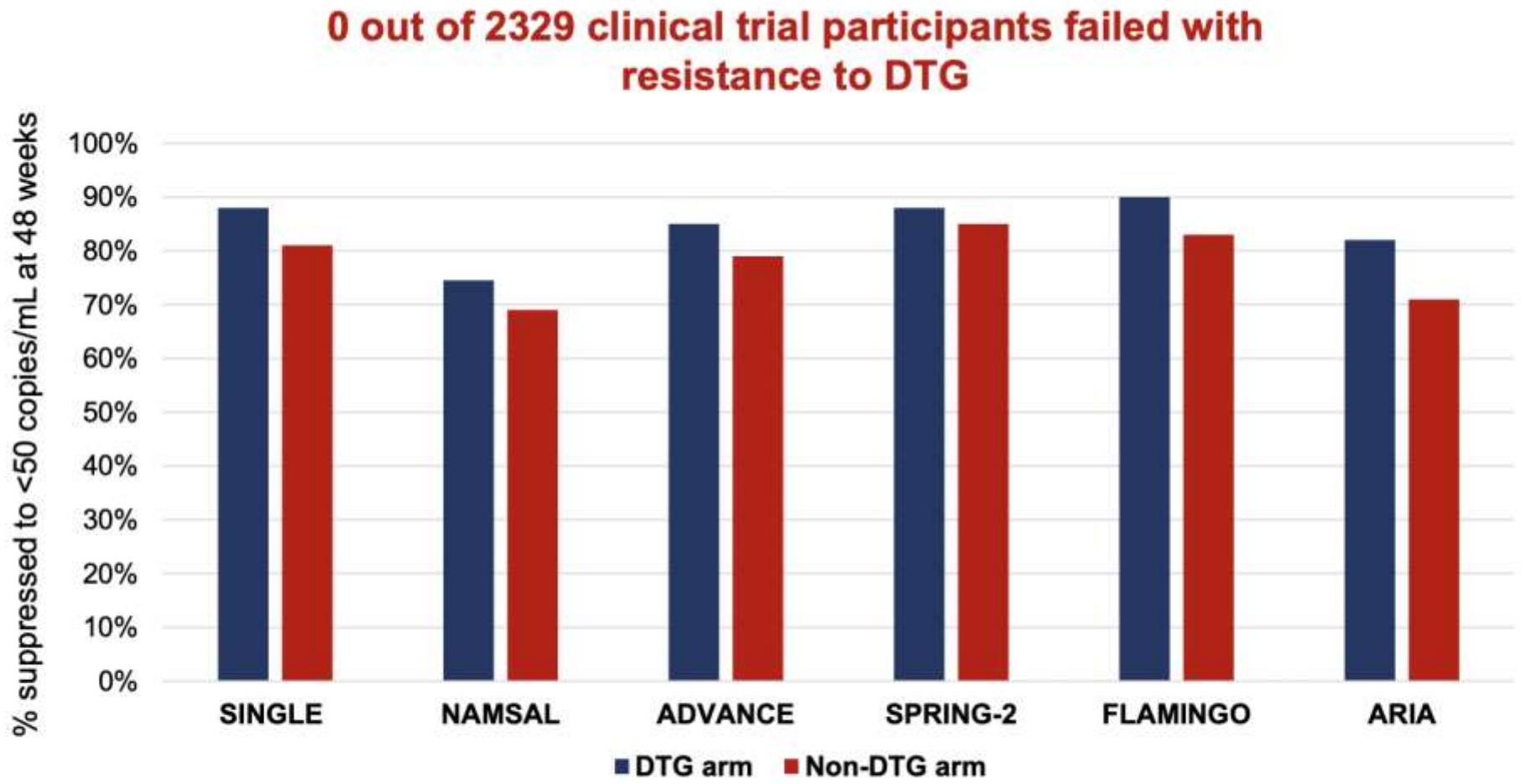
Bondarchuk 2022 Southern African Journal of HIV Medicine SA DOH ART Guidelines

Approach to virologic failure

- Inadequate adherence
- Drug resistance
  - Genotype requires VL >500-1000
  - Optimal if still on failing regimen because viruses constituting less than 10-20% not detected

- Consider drug-drug interactions
- Recent illness or vaccination?
- Poor absorption?

Dolutegravir as initial HIV therapy



Slide courtesy of S McCluskey, MGH

Walmsley SL, NEJM. 2013; NAMSAL ANRS 12313 Study Group, NEJM. 2019; Venter F, NEJM. 2019. Raffi F, Lancet. 2013; Clotet B, Lancet. 2014; Orrell C, Lancet HIV. 2017.

Resistance to DTG and BIC in First-Line Therapy

- For those receiving triple-therapy, a confluence of factors (clinical practice)
  - Advanced HIV disease based on labs and complications (3 cases)
  - Concomitant rifamycin (2 cases)
  - Poor adherence (1 case)
- For those receiving DTG/3TC (2 cases, clinical trials)
  - Poor adherence

Caveat: Much less experience with DTG/3TC as initial therapy in clinical practice

Slide courtesy of P Sax, BWH

Back to case – new information ! **POLL**

- 45 yo F with HIV diagnosed 5 y ago.
  - CD4 456, no OI.
- NHLS : Patient previously on TEE
  - 12 m after TEE VL was 14030 c/ml
- Referred for AEC and completed it
  - Repeat VL was 4320 c/ml then LTFU
- 2 y ago developed TB lymphadenitis. Started RIPE then TLD.
  - She achieved UD VL and TB cured.
  - However 6 m ago she had a VL of 2345 c/ml and was referred for adh. support
  - Today viral load is 3340 c/ml, CD4 345

What are 2 likely causes for viral load > 1000 on TLD, with history of virologic failure with TEE (i.e. TLD2)?

1. DTG resistance
2. Additional DTG 50 mg/day was not given
3. Poor ART absorption
4. Inadequate adherence
5. 1 and 4

Undisclosed prior ART use in South Africa

Some on “TLD1” not actually treatment naïve but may have cycled in & out of care

- Undisclosed prior ART use
- Forgot prior ART prior use / unaware of exposure to ART
- Received ART during pregnancy but lost to follow-up

In Limpopo, patients presenting for ART treatment initiation who reported no prior ART underwent baseline genotype hair analysis:

- 53% had ARVs in sample
- Genotype: 62% ≥1 DRM

Most sensitive databases in SA for prior ART use: NHLS (52%) or TIER.net (21%)

Mavhandu et al SA J of HIV Med 2021.

Sithole AIDS Behav. 2021

Management of VF on TLD in South Africa

Regimen	Definition	Resistance testing	Regimen change*
TLD-1	2 VL ≥1000 c/mL	Not recommended	Not recommended ABCDE & VL in 6m
TLD-2 < 2 years	2 VL ≥1000 c/mL	Not recommended	Not recommended ABCDE & VL in 6m
TLD-2 > 2 years	2 VL ≥1000 c/mL	Possibly - collaborate with HIV expert	→ Individualized regimen

* If CD4 <200 at virologic failure, collaborate w/ HIV expert South Africa ART Guidelines 2023

Mozambique (2/2): How common is DTG resistance in non-naïve patients at virologic failure in routine care?

Patients (N=716) previously on NNRT,I now on TLD with initial VL>1000

- 70% resuppressed after EAC
- 30% had confirmed VF (2 VL >1000)

- Genotyping performed in those with 2 VL>1000 on TLD

- 21% had resistance of intermediate / high-level to DTG incl. 118R (10%), 148H/R/K (5%), 263K (7%), 155H (3%)

✓ 10 (29%) of the 35 with DTG resistance had resistance to all 3 drugs in the regimen

✓ A RF for DTG resistance was an unsuppressed viral load at the time of switch to TLD

Bhatt et al AIDS Conference 2023

Case 2

POLL

- 52 yo man with HIV diagnosed 5 yrs ago with CD4 411, no OI
  - He received TEE & suppressed VL initially but developed virologic failure
  - For unclear reasons he left care
- Re-engaged 12 m ago. At that time CD4 254; he was initiated on TLD
  - Six months after TLD, viral load 32,400
  - Referred to EAC and he completed it
  - Today seen for follow-up VL of 24,800. No complaints. Exam: oral thrush

What would you do in clinic today?

(1) Restart prior TEE

(2) Recommend a limited treatment interruption

(3) Start cotrimoxazole and consult HIV expert

(4) Start fluconazole and continue TLD

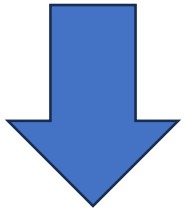
Most mortality in patients with VF occurs in those with *advanced HIV* at time of failure

- We looked at adults in the Western Cape who experienced VF during NNRTI era: 2012-17
- In 5748 patients with VF, there were 421 deaths
  - Median time from confirmed VF to death was ~7 months
- 78% of the deaths occurred in patients with adv. HIV (CD4 <200)
- 22% of deaths occurred in patients with higher CD4 counts

Gorrod JAIDS 2020

In patients with VF, remember: evaluate for presence of advanced HIV & need for OI prophylaxis / treatment

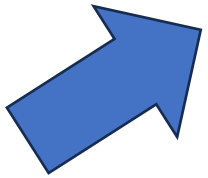
- Virologic failure often occurs at with <u>advanced HIV</u>
  - Recently, the median CD4 was ~250 at VF in South Africa



Obtain a CD4 count

Consider prophylaxis

Evaluate for TB/OI



For those with CD4 <200 cells/uL:

- Initiate cotrimoxazole
- Check CrAg and follow-up (+) test
- Obtain expert HIV consult. Why?
  - Discuss role for resistance test
    - Ex. prior ART with failure or transitioned to TLD when unsuppressed
  - Consider switch to boosted PI

Keene et al. J Acquir Immune Defic Syndr. 2023 SA ART Guidelines April 2023

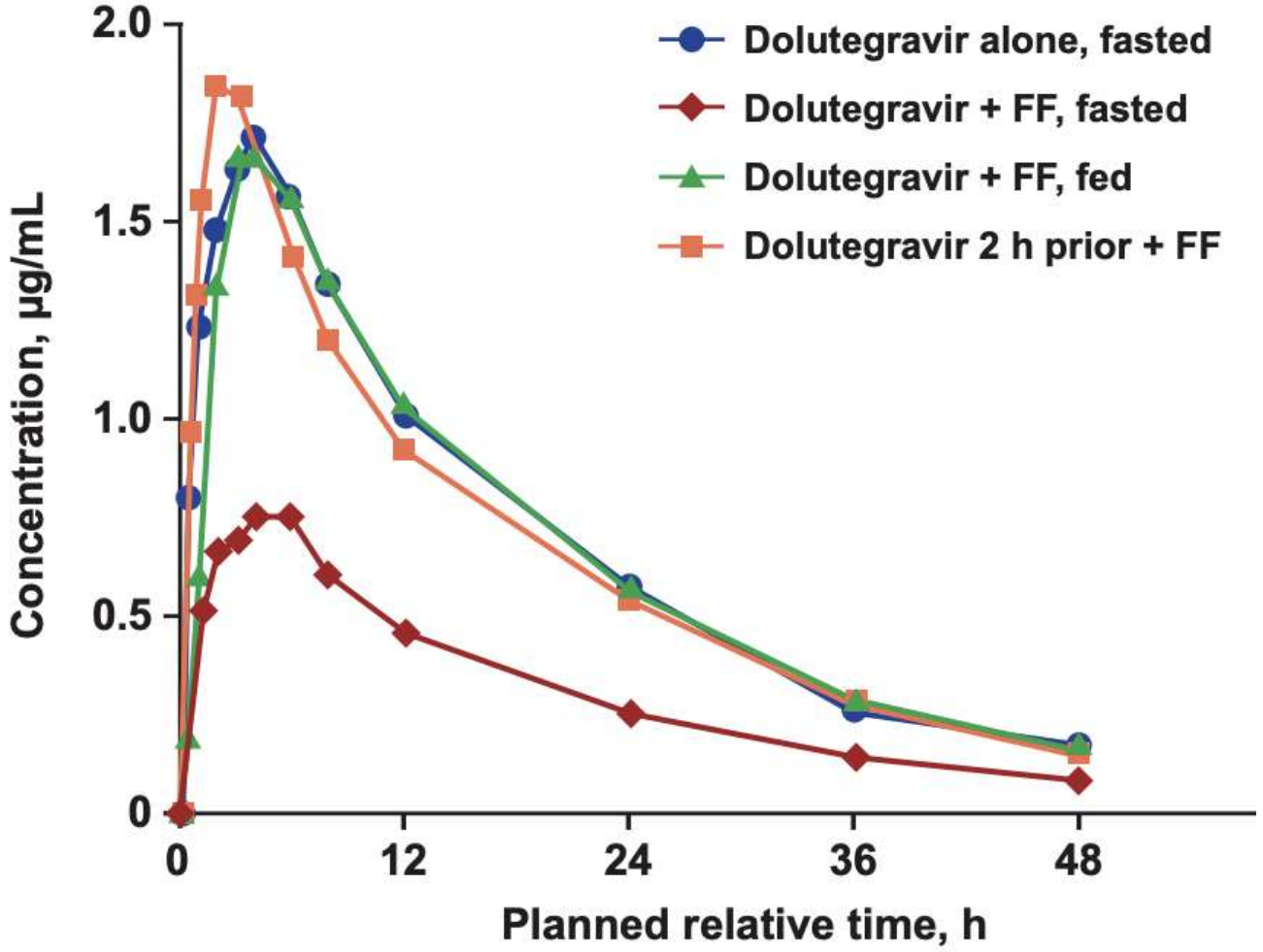
Approach to virologic failure

- Inadequate adherence
- Drug resistance
  - Genotype requires VL >500-1000
  - Optimal if still on failing regimen because viruses constituting less than 10-20% not detected

- Consider drug-drug interactions
  - Rifampicin lowers DTG conc.
  - Multivalent cations (for example, iron or calcium)
- Recent illness or vaccination?
  - Should not cause persistent viremia
- Poor absorption?
  - Very rare even w/ chronic diarrhea

Coadministration of DTG with Fe^{+2} or Ca^{+2}

- When DTG is given with iron or calcium, DTG plasma exposure is significantly reduced
  - Chelation: DTG * metal
- This can be overcome by separating the dosing
  - Take DTG 2 h before OR 6 h after
- It can also be overcome by the co-administration of DTG and minerals <u>with food</u>
- Not a major cause of VF



Song et al. The Journal of Clinical Pharmacology. 2015

SA study of HIV-associated TB:
Randomized to TLD vs TLD + DTG 50 mg/day

- TLD without additional + DTG 50 mg/day with rifampicin-based TB therapy may be adequate *(Griesel et al.* CROI, 2023)

- At 24 weeks (N=98), 83% patients in the TLD alone and 83% of patients in the TLD + DTG 50 mg/day achieved VL<50
  - Study not powered for comparison btwn arms

- Treating HIV/TB without additional + DTG 50 mg/day <u>does not appear</u> to be an important cause of virologic failure.
  - Caveat: Study too small to determine if there was a subtle effect

Griesel et al. CROI 2023

Approach to virologic failure

- Inadequate adherence
- Drug resistance

- Consider drug-drug interactions
- Recent illness or vaccination?
  - Can cause transient elevation in VL but not persistent viremia
- Poor absorption?
  - Very rare even w/ chronic diarrhea

Chronic diarrhea at ART initiation does not affect ART concentrations or virologic outcome

- It was previously suggested that high mortality of diarrhea in advanced HIV was caused by ART malabsorption
- In Haiti, concentrations of EFV, AZT and 3TC were compared in patients with and without chronic diarrhea (N=52, baseline CD4=60 cells)
- They measured ART levels at wks 2&4 plasma and at virologic outcomes

Antiretroviral drug concentrations and HIV-1 RNA levels in patients with and without diarrhea*

Measure	Patients with chronic diarrhea ($N = 26$)	Patients without chronic diarrhea ($N = 26$)	P value
Plasma zidovudine concentration (ng/mL) [IQR]	23.04 [BLD–74.36]	BLD [BLD–35.83]	0.07
Plasma lamivudine concentration (ng/mL) [IQR]	114.12 [79.54–175.51]	146.90 [78.72–194.57]	0.38
Efavirenz concentration (ng/mL) [IQR]	3066.32 [2361.55–6533.37]	3294.32 [1734.40–7069.68]	0.87
2-week change in $\log_{10}$ HIV-1 RNA level [IQR]	5.39 [5.09–5.93]	5.14 [4.7–5.43]	0.07
Proportion of participants with plasma HIV-1 RNA < 50 copies/mm^3 at 24 weeks	18/25 (72%)	16/24 (68%)	0.69

Dillingham et al. Amer J of Trop Med and Hygiene 2011

Conclusions

VF >1000 during TLD1 therapy	This affects as many as 5% of patients on TLD
Most common cause:	Inadequate adherence
New insight on low adherence	Most may not be forgetfulness/ access but intentional based on fears or mental health issues
Emerging cause of VF on TLD2?	DTG drug resistance
How common DTG resistance?	Possible 20% of those who have VL >1000 <u>despite</u> EAC
RF for DTG resistance?	- Prior VF on NNRTI or transition to TLD when viremic
	- Advanced HIV, low adherence, possibly rifampicin
Key tasks in at time of VF:	- Accurate treatment history (patient, databases)
	- Assess clinical status (new complaints, exam, CD4) & determine need for prophylaxis or treatment
Engage HIV expert	VF in patients on TLD2 or in persons with CD4<200

Thank you for listening.

Special thanks to….

- Peter Anderson
- Henry Sunpath
- Yunus Moosa
- Francois Venter
- Paul Sax
- Jienchi Dorward
- Nilesh Bhatt
- Suzanne McCluskey

Does EAC lead to re-suppression after VL >1000 c/ul in patients on TLD1?

- The ADVANCE trial randomized treatment naïve patients to DTG-based ART or to EFV-based ART
- Those who had VL>1000 referred rapidly for EAC
- In those with rebound VL >1000 after wk 24, time to resuppression shorter for DTG (12 wks) vs. EFV (26 wks)
- No cases of emergent DTG resistance in the individuals with viral load >1000 before resuppression