

# Tenofovir Diphosphate in Dried Blood Spots Predicts Virologic Failure and Resistance

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## BACKGROUND and OBJECTIVE

- Tenofovir diphosphate (TFV-DP) in dried blood spots (DBS) is a measure of cumulative adherence and drug exposure based on its 17-day half-life in red blood cells. This adherence measure is strongly associated with viral suppression and predictive of future viremia in persons with HIV (PWH).
- Moderately high concentrations of TFV-DP were observed in PWH who developed drug resistance within a clinical cohort. However, it remains unclear whether TFV-DP in DBS can predict virologic failure (VF) and drug resistance, in particular in resource-limited settings (RLS).

## METHODS

- A total of 1,000 treatment-naïve PWH >=18 years who initiated 1<sup>st</sup>-line ART (EFV or NVP + 2 NRTIs, most of them on TDF) at HIV clinics in peri-urban (RK Khan HIV Clinic in Chatsworth, N=500) and rural (Bethesda Hospital, N=500) setting in KwaZulu-Natal enrolled in parent study.
- Clinical follow-up occurred as per local standard of care. Participants could attend adherence counseling sessions. Medication Possession Ratio (MPR) was calculated using pharmacy refills.
- Cases were participants who developed VF (defined as and HIV RNA VL >=1,000 copies/mL after at least 5 months on ART). Cases were matched 2:1 with controls by age, gender, duration of ART and site. Blood for HIV genotyping and DBS was collected at the time when VF was identified in cases and corresponding time point for controls.
- HIV genotyping was performed using a validated in-house assay. TFV-DP in DBS was assayed using a validated LC-MS/MS method.
- One-way ANOVA was used to compare the concentrations of TFV-DP in DBS at the time of the last study visit between controls, participants with VF without resistance, participants with VF with resistance, and participants with VF in whom genotyping was unsuccessful (due to low HIV VL). Data are presented as mean [SD] or median (IQR).

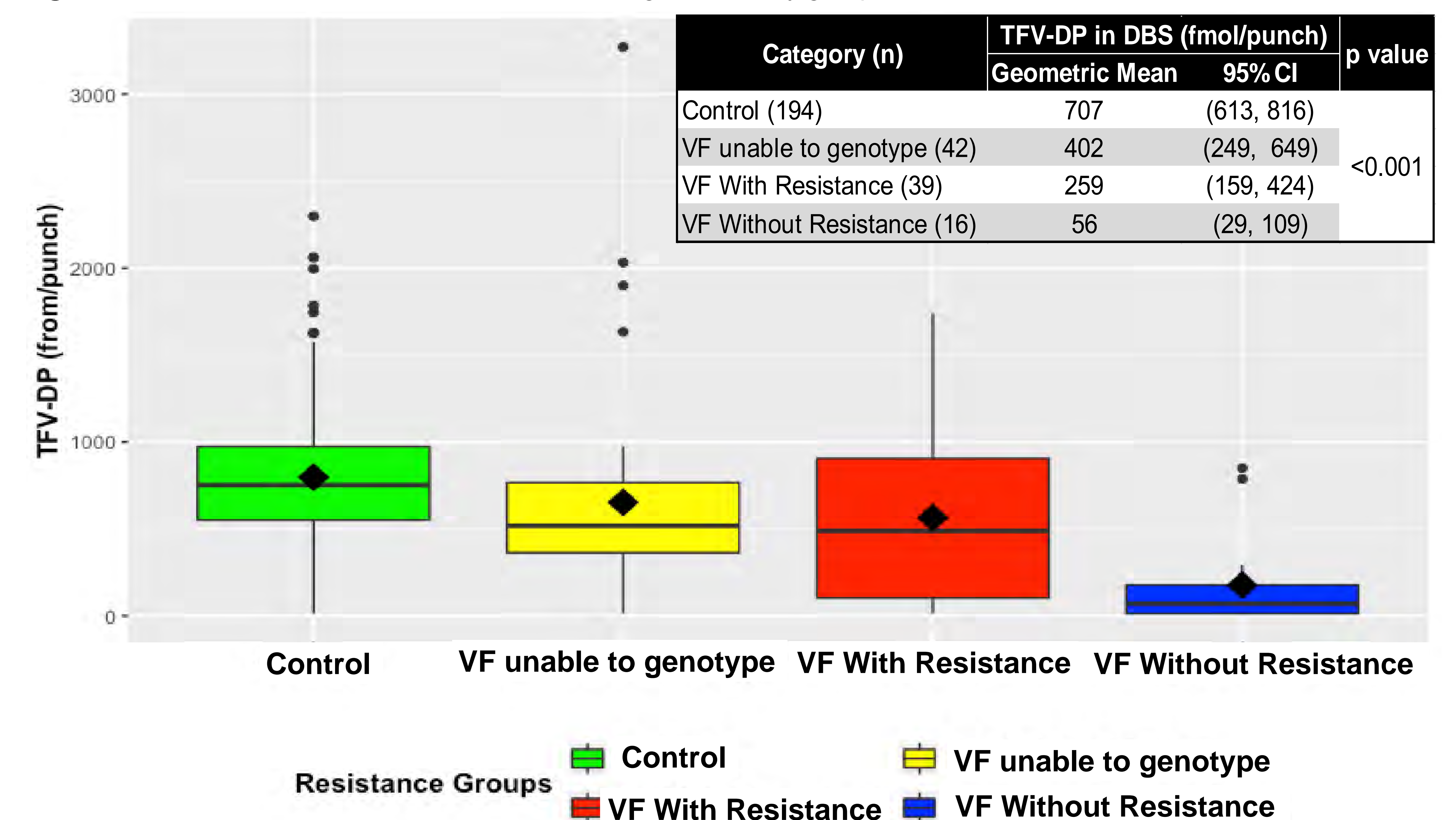
**Table 1.** Characteristics of the study population.

Characteristic	OVERALL (n=294)	CONTROL (n=197)	CASE (n=97)
<b>Age at enrollment</b>			
Median [IQR]	31 [26 - 39]	32 [27 - 39]	31 [25 - 40]
<b>Gender</b>			
Female	173/294 (59%)	119/197 (60%)	54/97 (56%)
Male	121/294 (41%)	78/197 (40%)	43/97 (44%)
<b>Ethnicity</b>			
Others	12/294 (4%)	5/197 (3%)	7/97 (7%)
Black	282/294 (96%)	192/197 (97%)	90/97 (93%)
<b>Have an ART supporter</b>			
No	29/285 (10%)	20/191 (10%)	9/94 (10%)
Yes	256/285 (90%)	171/191 (90%)	85/94 (90%)
<b>Any symptom felt related to ARVs</b>			
No	189/233 (81%)	122/151 (81%)	67/82 (82%)
Yes	44/233 (19%)	29/151 (19%)	15/82 (18%)
<b>Tuberculosis</b>			
Yes	12/294 (4%)	7/197 (4%)	5/97 (5%)
No	282/294 (96%)	190/197 (96%)	92/97 (95%)
<b>Recent CD4 count in cells/uL</b>			
Median [IQR]	371 [229 - 518]	416 [291 - 568]	268 [134 - 389]
<b>Recent CD4 count cells/uL</b>			
>=350	142/294 (48%)	112/197 (57%)	30/97 (31%)
<350	152/294 (52%)	85/197 (43%)	67/97 (69%)
<b>Recent HIV RNA VL copies/mL</b>			
Median [IQR]	41 [40 - 7,120]	40 [20 - 44]	39,100 [5,553 - 137,000]
<b>Duration of ART (months)</b>			
Median [IQR]	581 [323 - 912]	459 [302 - 821]	602 [344 - 986]
<b>Current Regimen</b>			
EFV/TDF/FTC	293/294 (99%)	197/197 (100%)	96/97 (99%)
Other	1/294 (<1%)	0/197 (0%)	1/97 (1%)
<b>Adherence counseling sessions</b>			
5+	31/285 (11%)	20/192 (10%)	11/93 (12%)
2-4	88/285 (31%)	59/192 (31%)	29/93 (31%)
0-1	166/285 (58%)	113/192 (59%)	53/93 (57%)
<b>Mobile phone</b>			
Yes	134/294 (46%)	89/197 (45%)	45/97 (46%)
No	160/294 (54%)	108/197 (55%)	52/97 (54%)
<b>MPR&gt;=0.9</b>			
Yes	264/294 (90%)	190/197 (96%)	74/97 (76%)
No	30/294 (10%)	7/197 (4%)	23/97 (24%)
<b>MPR&gt;=0.8</b>			
Yes	267/294 (91%)	190/197 (96%)	77/97 (79%)
No	27/294 (9%)	7/197 (4%)	20/97 (21%)
<b>MPR&gt;=0.7</b>			
Yes	271/294 (92%)	192/197 (97%)	79/97 (81%)
No	23/294 (8%)	5/197 (3%)	18/97 (19%)

TDF: tenofovir disoproxil fumarate; FTC: emtricitabine. EFV: efavirenz; ZDV: zidovudine (AZT); MPR: medication possession ratio.

## RESULTS

**Figure 1.** Concentrations of TFV-DP in DBS according to the study group.



\*One observation removed, Control Group, Value = 5703.78

Diamonds represent geometric mean (95% CI) TFV-DP concentrations. Boxes represent median (IQR) TFV-DP concentrations.

## CONCLUSIONS

- TFV-DP in DBS showed a step-wise association with VF and drug resistance in South African PWH on TDF-based ART, with drug concentrations that were approximately 2/3 lower in participants with VF and resistance compared to controls.
- PWH with VF who developed drug resistance had lower TFV-DP concentrations than those with VF in whom HIV genotyping was not successful (but higher than in those with VF and without resistance). This suggests that higher cumulative drug exposure may influence the ability to document drug resistance during VF.
- Future studies are required to determine whether TFV-DP in DBS can be used prospectively to monitor ART adherence and prevent VF, or if it can be used in lieu of drug resistance testing to determine the need for regimen modification in PWH failing first-line TDF-based ART.

## REFERENCES

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