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MAJOR ARTICLE

Clinical Outcomes Following the Use of Archived Proviral HIV-1 DNA Genotype to Guide Antiretroviral Therapy Adjustment

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Background. Evidence regarding the safety of using proviral HIV-1 DNA genotype (DNA GT) to guide antiretroviral therapy (ART) is limited. We hypothesized that HIV RNA would not increase following ART adjustment guided by DNA GT in a university HIV clinic.

Methods. Data were obtained from electronic medical records of adult persons living with HIV-1 (PWH) who underwent DNA GT testing and changed ART between October 2014 and November 2017. Logistic regression was used to evaluate the effect of ART switch on HIV RNA over time.

Results. Eighty-three PWH had DNA GT performed, 66 (80%) switched ART, and 59 had postswitch follow-up. Data were analyzed pre-/postswitch for these 59 PWH (median age, 54 years; 71% LWH ≥10 years; 46% ≥2 previous regimens; 36% recent low-level viremia; 34% unknown medication history). On DNA GT, 58% had ≥1-class ART resistance, 34% ≥2-class, and 10% 3-class. Median follow-up (range) was 337 (34–647) days. There was no change in probability of HIV RNA ≥50 copies/mL over time ($P > .05$). At baseline, 76% had HIV RNA <50 vs 88% at last postswitch follow-up ($P = .092$). Protease inhibitor use decreased from 58% to 24% ($P < .001$). Average daily pills and dosing frequency decreased from 3.48 to 2.05 ($P < .001$) and 1.39 to 1.09 ($P < .001$), respectively; ART cost did not change.

Conclusions. DNA GT facilitated changes in ART in a treatment-experienced population without increases in HIV RNA. Decreased pill burden occurred without increased ART cost. Further studies to identify optimal use of DNA GT are needed.

Keywords. HIV; archived proviral HIV DNA genotype; antiretroviral therapy; genotypic antiretroviral resistance testing; peripheral blood mononuclear cell DNA.

People living with HIV (PWH) currently require lifelong antiretroviral therapy (ART) to maintain viral suppression, restore immunologic function, prevent transmission, and reduce HIV-related morbidity and mortality. Long-term complications such as decreased bone density, chronic kidney disease, and cardiovascular events have become a burden for PWH, and some are a result of ART [1–3]. ART options for HIV have expanded to include agents with more favorable long-term safety profiles, fewer drug interactions, and reduced pill burden [4, 5]. However, current treatment guidelines recommend caution when switching ART unless there is evidence from historical resistance profiles or medication history that the new regimen will be fully active [5, 6]. Transmitted drug resistance (TDR) occurs in ~10%–17% of treatment-naïve PWH, and drug resistance-associated mutations (RAMs) are more common in treatment-experienced individuals [5–7]. HIV genotype is recommended at care entry to assess for TDR, or in the setting of virologic failure [5–7]. When HIV is well controlled, resistance testing may also be necessary for ART adjustment. However, standard HIV genotype involves sequencing of plasma HIV RNA and typically requires levels ≥500 copies/mL. During the process of infecting host CD4+ T lymphocytes, HIV is integrated into the host genome as proviral DNA. Some of these CD4 cells survive infection, and latent proviral DNA in these cells can represent an archive of viral mutations that have emerged throughout the course of infection. Proviral DNA can be detected in peripheral blood mononuclear cells (PBMCs) when plasma HIV RNA levels are undetectable, extracted and amplified by polymerase chain reaction (PCR), and analyzed with next-generation sequencing of the HIV-polymerase region to identify mutations

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present for nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), integrase inhibitors (INSTIs), and protease inhibitors (PIs) [8].

Department of Health and Human Services (DHHS) HIV treatment guidelines and the International Antiviral Society (IAS) note that proviral DNA resistance assays may be useful for individuals with prior treatment failure or prolonged ART history when genotypic tests are not available, but their utility is undetermined, and they should be utilized in conjunction with treatment history [5, 6]. RNA genotype (RNA GT) results can be affected by viral population changes and selective drug pressure, as can the DNA compartment. Possible limitations to proviral DNA genotype (DNA GT) include the potential for delayed identification of emerging resistance, insensitivity to low-frequency mutations, and the potential for sequencing nonviable variants that lack clinical significance [9, 10].

Evidence for DNA GT has primarily been limited to studies designed to assess concordance with historical RNA GT [11–24]. The objective of this retrospective study was to assess clinical outcomes following ART adjustment guided by information from DNA GT. We hypothesized that HIV RNA would not increase following ART adjustment guided by DNA GT.

METHODS

Study Design and Population

This study was conducted at a Ryan White–funded university HIV clinic in southern Arizona. In this clinic, ~1000 PWH are routinely seen by a team consisting of an infectious diseases physician, an HIV pharmacist, and a clinical coordinator. This study was approved by the University of Arizona Institutional Review Board (IRB), and informed consent was waived because the study was retrospective and involved no more than minimal risk to subjects. Study procedures were conducted in accordance with the Declaration of Helsinki. We reviewed the electronic medical records (EMRs) of adult (≥18 years of age) PWH who underwent DNA GT testing and changed ART between October 2014 and November 2017 and presented for follow-up labs. PWH were excluded if they were pregnant.

Data and Outcomes

Medical and laboratory data were extracted from the EMR. Data collected included demographics, year of HIV diagnosis, history of AIDS, history of opportunistic infection (OIs) within the previous year, and comorbid conditions (including mental health diagnosis, defined as documented mental health diagnosis; history of atherosclerotic cardiovascular disease [ASCVD], defined as documented history of ASCVD; hypertension [HTN], defined as documented HTN diagnosis or current treatment with antihypertensive agents; chronic kidney disease [CKD], defined as documented CKD diagnosis; diabetes mellitus [DM], defined as documented DM diagnosis or current treatment with antidiabetic agents; and substance use disorder, defined as documented active substance use disorder). Other data collected included current statin use, historical genotype/phenotype data, DNA GT results, reason for obtaining DNA GT, HIV RNA values, absolute and percent CD4 counts, components of pre-/postswitch ART regimens including number of pills per day, frequency, and ART classes, and documented nonadherence, defined as a note from a care team member indicating that the patient reported nonadherence. ART price was determined using the average wholesale (AWP) price per month listed in the DHHS guidelines [5].

DNA GT was performed using the GenoSure Archive (Monogram Biosciences). This is a next-generation sequencing–based assay for genotyping proviral DNA, which generates consensus sequences for mutations present in ≥10% of the viral species [8]. The Stanford HIV Drug Resistance Database was used for drug resistance interpretation [7]. Resistance to an ART class was defined as high-level resistance to at least 1 drug in the class. Preswitch and postswitch regimen genotypic susceptibility scores (GSS) were calculated using RAMs from DNA GT and historical RNA GT when available. For each antiretroviral, a GSS value was assigned based upon Stanford resistance interpretation (GSS value 0 for high-level resistance, GSS value 0.5 for intermediate or low-level resistance, GSS value 1 for potential low-level resistance or susceptible).

Statistical Analyses

Plasma HIV RNA was compared before and after switching ART. For the primary outcome, HIV RNA values were evaluated over time. HIV RNA values were dichotomized to values ≥50 copies/mL or <50 copies/mL. The dichotomized postswitch HIV RNA values were fit to a logistic regression model with fixed effects for days postswitch (centered and scaled for a better model fit), whether preswitch HIV RNA was ≥50 copies/mL or <50 copies/mL, and nonadherence. The interaction between "days postswitch" and "preswitch HIV RNA" was also included as a fixed effect to allow for the possibility that the timing of HIV RNA becoming ≥50 copies/mL after switching may differ between those who had HIV RNA <50 copies/mL or ≥50 copies/mL before switching. The model was fit using generalized estimating equations and an exchangeable covariance structure to account for the correlation among data points from the same patient [25, 26].

Secondary outcomes included percentage of PWH with HIV RNA <50 or <200 copies/mL at initial and last follow-up compared with baseline, change in CD4 counts, and pre-/postswitch comparison of ART components, price, and pill burden. Differences between historical genotypes and DNA GT for individuals were described. Finally, PWH who required ART adjustment again after the original switch were identified and reasons assessed. Comparisons of categorical variables at 2 time points were conducted using McNemar's test. Paired

comparisons of medians were conducted using the Wilcoxon signed-rank test, and paired comparisons of means were conducted using paired *t* tests. *P* values for pill burden (pill number and frequency pre–/post–ART switch) and GSS score pre–/post–ART switch were calculated from binomial distributions (described in the Supplementary Data). Statistical significance was defined as 2-sided *P* values <.05.

RESULTS

Patient Characteristics

A total of 88 PWH had DNA GT ordered; of these, 2 did not complete the order, 3 had assay failure, 83 had DNA GT successfully performed, 66 (80%) changed ART, and 59 had follow-up during the study period and are included in the analyses. Reasons for not changing ART (n = 17) included patient preference (29%), multiclass resistance on DNA GT (24%), provider had another reason unrelated to drug resistance (24%), DNA GT confirmed susceptibility to current regimen (18%), and patient did not follow up (6%). Baseline characteristics of the 59 PWH who changed ART are shown in Table 1. Most were male (85%), white (66%), and the median CD4 cell count was 544/μL. The majority had longstanding infection; 71% had been living with HIV for ≥10 years, and 47% had a history of AIDS. There were significant comorbidities in this population; 61% had a mental health diagnosis, 31% had history of ASCVD, and 20% had CKD. Although the rationale for obtaining DNA GT was not always documented, 46% had been on 2 or more previous regimens, 36% had recent HIV RNA ≥50 copies/mL with RNA levels insufficient for RNA GT, 34% lacked a complete ART history, and 8% had none of these characteristics documented. DNA GT revealed 1-class ART drug resistance in 58% and 3-class resistance in 10%. Five had at least 1 darunavir RAM, 2 had high-level darunavir resistance, and 5 had INSTI resistance.

Nine PWH had historical RNA GT available for comparison (Table 2). Five had concordant resistance profiles between DNA GT and historical GT. Two DNA GT failed to detect M184V mutations identified previously on RNA GT. In 3 cases, DNA GT detected RAMs that were not detected on prior RNA GTs, including RAMs in the reverse transcriptase (RT) and integrase regions.

Plasma HIV RNA Outcomes

First follow-up and last follow-up HIV RNA testing occurred a median (range) of 60 (13–552) and 337 (34–647) days after switching ART, respectively. At baseline, 76% had HIV RNA <50 copies/mL, compared with 83% at first follow-up (*P* = .388) and 88% at last follow-up (*P* = .92) (Table 3). Using a higher HIV RNA cutoff, 92% at baseline had HIV RNA <200 copies/mL compared with 95% at both first and last follow-up (*P* = .687). Of the 45 PWH who had HIV RNA <50 copies/mL at baseline, 41 (91%) maintained HIV RNA <50 copies/mL at the first follow-up and 42 (93%) had HIV RNA <50 copies/mL at last follow-up. Of the 14 PWH with HIV RNA ≥50 copies/mL at baseline, 10 (71%) achieved HIV RNA <50 copies/mL at last follow-up. Information about the 7 PWH with HIV RNA ≥50 copies/mL at last follow-up is shown in Supplementary Table 1. Of these 7, 4 were nonadherent (3 of whom had an HIV RNA ≥200 copies/mL at last follow-up), and none had evidence of new resistance mutations on repeat RNA GT.

In the logistic regression model, which was the primary outcome of the study, there was no statistically significant change in the probability of having HIV RNA ≥50 copies/mL over time, meaning that the number of days postswitch did not impact postswitch HIV RNA. The effect of time was not present in the interaction (odds ratio [OR], 0.64; 95% confidence interval [CI], 0.25–1.62; *P* = .345) or main effect (OR, 1.21; 95% CI, 0.58–2.54; *P* = .618) (Table 4). Nonadherence and preswitch HIV RNA ≥50 copies/mL were associated with a higher probability of having HIV RNA ≥50 copies/mL over time (OR, 8.38; 95% CI, 2.08–33.76; *P* = .003; and OR, 13.31; 95% CI, 3.40–52.12; *P* < .001, respectively). Table 5 details model-estimated probabilities of detectability at 12 and 24 weeks postswitch for various combinations of predictors. For adherent individuals with preswitch HIV RNA <50 copies/mL, the probability of having HIV RNA ≥50 copies/mL at 24 weeks postswitch was 0.03 (95% CI, 0.01–0.10). Conversely, for nonadherent individuals with a preswitch HIV RNA ≥ 50 copies/mL, the probability was 0.82 (95% CI, 0.52–0.95).

Twelve PWH had their ART switched more than once (6 who had HIV RNA <50 copies/mL preswitch and 6 who had ≥50 copies/mL preswitch). Four of these 12 PWH switched from TDF to TAF, with all other ART remaining the same. One switched due to provider preference for an NRTI-sparing regimen, 1 underwent stepwise simplification, and 1 switched due to side effects. Three had low-level viremia (HIV RNA 50–200 copies/mL) during follow-up and either added an agent, changed NRTIs, or changed from an NNRTI- to INSTI-based regimen. Only 2 PWH who switched again ever had HIV RNA ≥200 copies/mL, and both had started with HIV RNA ≥50 copies/mL preswitch. One of these 2 reported 0% adherence and had no new mutations on repeat RNA GT. The second had complicating comorbid factors and elevated HIV RNA despite no additional RAMs on multiple repeat RNA GT. This person ultimately achieved HIV RNA <50 copies/mL despite de-escalating therapy. A post hoc analysis was performed to determine the impact of HIV RNA values collected after switching ART again. Removing these HIV RNA values from the primary analysis yielded similar results (Supplementary Table 2).

Secondary Outcomes

There was no statistically significant change in CD4 counts over time (*P* = .595); median CD4 count (range) at last follow-up was 578/μL (211–1672/μL). ART pill burden decreased significantly postswitch. The average number of pills per day decreased from

Table 1. Characteristics of Study Patients (n = 59)

Characteristic	Patients, No. (%)[a]
Age, median (range), y	54 (25–73)
Male sex	50 (85)
Race	
White	39 (66)
African American	5 (8)
Asian	1 (2)
American Indian	1 (2)
Ethnicity	
Hispanic or Latino	13 (22)
Time since HIV diagnosis, median (range), y	17 (3–35)
≥10 y since HIV diagnosis	42 (71)
Documented AIDS diagnosis	28 (47)
Documented opportunistic infection within previous year	0 (0)
Mental health diagnosis	36 (61)
Atherosclerotic cardiovascular disease	18 (31)
Hypertension	15 (25)
Chronic kidney disease	12 (20)
Diabetes mellitus	7 (12)
Substance use disorder	4 (7)
Statin therapy	22 (37)
Preswitch CD4 count, median (range), cells/μL	544 (185–1720)
<200 cells/μL	2 (3)
200–349 cells/μL	7 (12)
350–499 cells/μL	17 (29)
≥500 cells/μL	33 (56)
Preswitch HIV RNA	
<50 copies/mL	45 (76)
50–199 copies/mL	9 (15)
≥200 copies/mL	5 (8)
Median (range) HIV RNA if ≥200 copies/mL	531 (216–16 300)
Preswitch ART regimen characteristics	
Regimen contained NRTI	54 (92)
Regimen contained NNRTI	20 (34)
Regimen contained PI	34 (58)
Regimen contained INSTI	27 (46)
No. of pills/d, mean +/- SD	3.48 +/- 2.05
Frequency of dosing/d, mean +/- SD	1.39 +/- 0.49
GSS, median (range)	3 (0.5–4)
GSS <2	8 (14)
GSS 2–2.5	18 (31)
GSS ≥ 3	33 (56)
ART resistance present on proviral DNA genotype before switch	
Wild-type (no RAMs)	13 (22)
≥1-class resistance[b]	34 (58)
≥2-class resistance[b]	20 (34)
3-class resistance[b]	6 (10)
NRTI resistance[b]	25 (42)
NNRTI resistance[b]	25 (42)
PI resistance[b]	5 (8)
INSTI resistance[b]	5 (8)
M184V	23 (39)
At least 1 DRV RAM	5
High-level DRV resistance	2
High-level resistance to RAL and/or EVG	5
High-level resistance to DTG	1
Partial resistance to RAL and/or EVG	2
Partial resistance to DTG	2

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; EVG, elvitegravir; DRV, darunavir; DTG, dolutegravir; GSS, genotypic susceptibility score; INSTI, integrase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitor; RAL, raltegravir; RAM, resistance-associated mutation.

[a]Data represent No. (%) of patients unless otherwise specified.

[b]Defined as high-level resistance to at least 1 agent in the antiretroviral class.

3.48 to 2.05 ($P < .001$), and the average frequency decreased from 1.39 to 1.09 times per day ($P < .001$). ART regimen components were compared pre-/postswitch. The median regimen GSS (range) was 3 (0.5–4) preswitch and 3 (1.5–3) postswitch. There was no significant change in GSS overall ($P = .093$). The proportion with GSS <2 decreased from 8 (14%) preswitch to 2 (3%) postswitch ($P = .031$), and the proportion with GSS ≥3 increased from 33 (56%) to 41 (69%; $P = .039$). The number of PWH taking PIs decreased from 34 (58%) to 14 (24%) postswitch ($P < .001$), and the number taking INSTIs increased from 27 (46%) to 50 (85%; $P < .001$). There were no significant differences in the number of PWH taking NNRTIs or NRTIs. Four PWH discontinued older PIs (fosamprenavir and lopinavir), and 7 discontinued efavirenz. Tenofovir alafenamide (TAF) became available in the United States during the study period, and many switched from tenofovir disoproxil fumarate (TDF) to TAF; the percentage on TDF decreased from 73% to 8%, and the percentage on TAF increased from 2% to 80% ($P < .001$ for both comparisons). There was no significant difference in the price of ART; the average monthly ART price was $4093.56 preswitch and $4043.05 postswitch ($P = .717$).

DISCUSSION

This study is the first to describe clinical outcomes related to the use of DNA GT to guide ART adjustment. DNA GT was performed in <8% of patients seen in the clinic over a 3-year period, and the majority (80%) who underwent DNA GT testing switched ART. As a group, these were older individuals with an extensive history of HIV infection and multiple ART regimens, and most had HIV RNA <50 copies/mL at baseline. Consistent with our initial hypothesis, there was no statistically significant change in the probability of an individual having HIV RNA ≥50 copies/mL over time after DNA GT–guided ART switch. Furthermore, only 4 PWH had virologic failure (HIV RNA > 200 copies/mL) at any time point after ART switch, and 3 of these had follow-up RNA GT performed, with no evidence of additional RAMs compared with their original DNA GT. ART nonadherence rather than RAMs was the more likely cause of persistently elevated HIV RNA, and nonadherence was strongly correlated to RNA >0 copies/mL.

Table 2. Comparisons Between DNA Genotype and Historical RNA Genotypes

Patient	No. and Type of Historical Genotypes[a]	Time Between Historical and DNA Genotype, d	Resistance Mutations on Historical Genotype[b]	Resistance Mutations on DNA Genotype[b]
1	1 RNA GT	1632	*RT:* M41L, T69N, K103R *PR:* I13V	*RT:* M41L, T69N, K103K/R *PR:* M46M/I, I13I/V
2	1 RNA GT	761	*RT:* M184I, K101E, G190A, V90I *PR:* L90M	*RT:* M184M/V, K101E/K, G190G/A, V90V/I *PR:* L90M
3	1 RNA GT	763	*RT:* **M184V** *PR:* E35D	*RT:* **K103K/R**, **E138E/G** *PR:* E35D, I62I/V *IN:* I203M
4	3 RNA GT	591, 623, 885	*RT:* V179I *PR:* I62V	*RT:* V179V/I *PR:* I62I/V, I13I/V
5	2 RNA GT 2 IN RNA GT	268, 427 268, 427	*RT:* M184V *IN:* E138K, Q148R	*RT:* M184M/I/V, V118V/I *PR:* E35D, M46M/I *IN:* E138E/K, **S147S/G**, Q148Q/R
6	2 RNA GT 1 IN RNA GT	513, 858 513	*RT:* T69N, Y181C, V179I *PR:* D60E *IN:* T97A	*RT:* T69T/N, **L74L/V**, **M184M/V**, **L100L/I**, **K103K/N**, Y181Y/C, V90V/I, V179V/I *PR:* D60D/E, I62I/V, I85I/V *IN:* T97T/A, **N155N/H**
7	1 RNA GT	915	*RT:* T215S, V179D/E *PR:* E35D, M36I, I62V, A71V	*RT:* V179D/E/I *PR:* E35D, M36I, I62V, A71V
8	1 RNA GT 1 IN RNA GT	0[c] 35	*RT:* **M184V** *PR:* M36I, L63T, L89M *IN:* N155H	*PR:* E35E/D, M36I, L63T, L89M *IN:* N155N/H
9	2 RNA GT	749, 1069	*PR:* D60E, I62V, I13I	*PR:* D60E, I62V, I13I

Abbreviations: GT, genotype; IN, integrase; PR, protease; RT, reverse transcriptase.

[a]All historical RNA GT utilized Sanger sequencing.

[b]Resistance-associated mutations affecting concordance for drug susceptibility are bolded.

[c]"Historical" RNA GT was drawn on the same day as DNA GT.

Preswitch HIV RNA ≥50 copies/mL was also correlated to HIV RNA ≥50 copies/mL postswitch, possibly related to undocumented nonadherence or other baseline factors (such as comorbid conditions or multiple-class ART resistance). However, the majority (71%) of the PWH with preswitch HIV RNA ≥50 copies/mL achieved HIV RNA <50 copies/mL at last follow-up. DNA GT results facilitated switches to more favorable regimens with fewer potential drug interactions, which was important for this older population, many of whom had comorbidities. Based upon GSS score results, there was a tendency toward more robust regimens postswitch. Pill burden improved postswitch without an increase in ART cost.

Early studies of the concordance between PBMC proviral DNA and plasma RNA genotype found a strong correlation between assays but fewer RAMs detected in proviral DNA [12–14]. There have been changes to proviral DNA assays since then, including incorporation of next-generation sequencing, which has improved the sensitivity to detect low-level minor variants [8, 27–29]. A next-generation sequencing–based prototype of the DNA GT used in our study was used to retrospectively perform DNA GT on frozen baseline PBMC samples from 51 virologically suppressed PWH enrolled in the Switching Boosted PI to Rilpivirine in Combination with Truvada as a Single-Tablet Regimen (SPIRIT) study [30]. All subjects had historical RNA GT demonstrating susceptibility to rilpivirine, emtricitabine, and tenofovir. DNA GT detected 89% of RAMs on RNA GT. Historical RNA and baseline DNA GT were concordant for the 4 patients who had experienced virologic failure with resistance, except that DNA GT identified Y181C and M184I missed by baseline RNA GT for 1 patient. A recent study that used the same DNA GT assay as our study reported higher levels of concordance in treatment-experienced PWH with an average of 7 historical GTs; they observed 89% sensitivity to detect historical resistance mutations and 85% overall susceptibility concordance (NNRTIs 93%, PIs 84%, NRTIs 76%) [23]. Another study demonstrated that concordance may be

Table 3. Patients With HIV RNA <50 Copies/mL and <200 Copies/mL at Various Time Points

Value	Patients Preswitch, No. (%)	Patients at First Follow-up, No. (%)	*P*[a]	Patients at Last Follow-up, No. (%)	*P*[b]
HIV RNA <50 copies/mL	45 (76)	49 (83)	.388	52 (88)	.092
HIV RNA <200 copies/mL	54 (92)	56 (95)	.687	56 (95)	.687

[a]Comparison between number of patients with HIV RNA below stated value at first follow-up vs preswitch. Median time to first follow-up (range) was 60 (13–552) days after switching medications.

[b]Comparison between number of patients with HIV RNA below stated value at last follow-up vs preswitch. Median time to last follow-up (range) was 337 (34–647) days after switching medications.

Table 4. Primary Outcome Analysis: Logistic Regression Model of Whether HIV RNA ≥50 Copies/mL Over Time

Predictor	OR (95% CI)	*P*
Days postswitch	1.21 (0.58–2.54)	.618
Preswitch HIV RNA ≥50 copies/mL	13.31 (3.40–52.12)	<.001
Documented nonadherence	8.38 (2.08–33.76)	.003
Days postswitch × preswitch HIV RNA ≥50 copies/mL	0.64 (0.25–1.62)	.345

Abbreviations: CI, confidence interval; OR, odds ratio.

decreased in individuals with longer periods of ART treatment [31], whereas a cohort study of viremic patients on ART for a median of 7 years found 84% concordance between DNA and RNA GT [24]. There were 3 cases in our study in which DNA GT identified RAMs not present on historical genotypes. This could have been related to the development of new resistance and ART exposure over time [21]. In addition, DNA GT did not identify M184V in 2 cases with known M184V on historical GT. In 1 of these cases, DNA GT was drawn on the same day as the RNA GT. The authors of a recent abstract reported that the same DNA GT assay used in our study missed 52% of historically documented M184V mutations in their population [32]. This could be related to decreased fitness of the virus with M184V substitution, assay cutoffs, or sampling limitations [33]. Given the current lack of clinical data and evidence that RNA and DNA GT are not always fully concordant, DNA GT results should be interpreted with caution and correlated with historical genotypes, treatment history, regimen potency, and patient-specific factors.

Table 5. Model-Estimated Probabilities of Detectability for Various Combinations of Predictors

Predictor Combination	12 Weeks Postswitch Estimated Probability of HIV RNA ≥50 Copies/mL (95% CI)	24 Weeks Postswitch Estimated Probability of HIV RNA ≥50 Copies/mL (95% CI)
Preswitch HIV RNA <50 copies/mL No documented nonadherence	0.03 (0.01–0.10)	0.03 (0.01–0.10)
Preswitch HIV RNA ≥50 copies/mL No documented nonadherence	0.38 (0.18–0.63)	0.35 (0.17–0.59)
Preswitch HIV RNA <50 copies/mL Documented nonadherence	0.21 (0.07–0.50)	0.23 (0.09–0.47)
Preswitch HIV RNA ≥50 copies/mL Documented nonadherence	0.84 (0.54–0.96)	0.82 (0.52–0.95)

Abbreviation: CI, confidence interval.

The role of DNA GT in clinical practice remains unclear. It is unlikely that DNA GT will provide additional information in individuals receiving their first or second ART regimen who have not experienced virologic failure. Given the development of more potent ART options, current low levels of baseline resistance to firstline INSTI, and increasing evidence that 2-drug or NRTI-sparing regimens may be safe, the utility of DNA GT may decrease [5]. Most individuals in this study were on ≥2 previous regimens, had unknown treatment history, or had recent low-level viremia, suggesting that these characteristics may have been motivating factors for utilizing DNA GT in this population. In addition, most PWH included had resistance to at least 1 antiretroviral class (58%) and had been living with HIV for at least 10 years (71%). DNA GT may be useful for ART-experienced populations with comorbid conditions, multiple medication interactions (such as history of transplant, anticoagulation, or mental health disorders), difficulty accessing care, patient hesitancy regarding ART switches, or other factors that could increase the risks associated with multiple ART adjustments. Cost of the DNA GT, which may decrease over time, should also be a consideration.

There were several limitations to this study. It was notable that 12 PWH switched ART more than once, and HIV RNA values after subsequent switches were included in the analyses. We performed a post hoc analysis, removing values after the secondary switch, and found similar results. Due to the retrospective design, follow-up duration varied. Some PWH, such as those who switched ART toward the end of the study period, did not have follow-up labs and were not included. This could have led to attrition bias. Small sample size was a limitation of this study. It was also conducted at a single center and could lack generalizability to other populations. This study was observational and therefore lacked a formal control group. Finally, for our primary outcome, the lack of a significant finding does not definitively prove the lack of an effect. However, all analyses were consistent in demonstrating that there was no postswitch increase in number of patients with HIV RNA ≥50 copies/mL or in the probability of having HIV RNA ≥50 copies/mL over time.

In conclusion, proviral DNA GT provided additional information to facilitate switching ART in a treatment-experienced population. ART changes guided by DNA GT did not lead to virologic failure and likely contributed to improved long-term safety and quality of life [34–40]. Further studies are needed to define the optimal clinical application of the DNA GT assay.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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