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HIV-1 DNA Resistance Testing Informs the Successful Switch to a Single Tablet Regimen

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Abstract

Background: HIV-1 DNA drug resistance testing is increasingly used to guide antiretroviral (ARV) regimen switches in the setting of viral suppression. In this single-arm study, HIV-1 DNA resistance testing was used to assess eligibility for the fixed-dose combination of abacavir/dolutegravir/lamivudine in the context of a switch study evaluating changes in bone mineral density in HIV-1 positive adults ages 50 years and older.

Methods: Study subjects had viral loads which were <50 copies/mL at study screening. Susceptibility to each component of the switch regimen was assessed using an HIV-1 DNA genotypic resistance assay. A regimen switch was made only when the subject's virus was sensitive to each component of the switch regimen. Viral load measurements were obtained per study protocol through weeks 24 and 48.

Results: At week 24, the HIV-1 RNA viral load was <50 copies/mL for 44 of 44 study participants with available follow-up data, (95% CI [0.920, 1]). At week 48, 41 of 42 participants were virologically suppressed to <50 copies/mL, (95% CI [0.874, 0.999]); 1 participant had a viral load of 62 copies/mL.

Conclusion: In this pre-selected population of virologically suppressed patients, HIV-1 DNA resistance testing successfully identified candidates for ARV treatment modification to an available single tablet regimen. These results support the utility of HIV-1 DNA drug resistance testing in the clinical setting.

Keywords: HIV-1 DNA drug resistance test • Proviral assay • Switch study • Viral suppression

Introduction

Over the course of the HIV epidemic, advances in ARV drug development have resulted in dramatic improvements in potency and efficacy while lowering toxicity and pill burden. These improvements have contributed to a US national viral suppression rate of 59.8% in 2015 [1] and even higher reported rates for 2017 among persons who received an HIV positive diagnosis [2]. However, despite these significant advancements, long-term use of ARV drugs may result in major side-effects including renal impairment, cardiovascular disease, lipodystrophy, osteoporosis and other co-morbidities. Given these potentially unfavourable long-term outcomes, healthcare providers may choose to modify patient treatment regimens to avoid or decrease the severity of ARV drug side-effects.

According to the CDC, nearly half of the HIV-infected population in the United States are age 50 and older [3]. Within this older HIV-infected population, it is important to closely monitor and manage medications that could negatively contribute to or worsen pre-existing health conditions because of the greater incidence of comorbidities, non-AIDS complications, and frailty [4]. In 2001, tenofovir disoproxil fumarate (TDF) received FDA approval for the treatment of HIV. Since then, TDF has remained a recommended antiretroviral as part of a multi-drug HIV treatment regimen due to favorable potency, tolerability and half-life. However, prolonged TDF use has been associated with decreased bone mineral density (BMD) and kidney dysfunction [5-7]. Guidelines issued by the Department of Health and Human Services (DHHS) state that in older (≥50 years) HIV-positive adults at risk for or with declining bone density and kidney related health issues being treated with TDF, switching to regimens that do not contain TDF should be considered [4]. Tenofovir alafenamide (TAF) is a recently approved pro-drug formulation of tenofovir with less impact on bone and kidney function compared to TDF [8]. However, the long-term effects of TAF are still unclear, particularly in older HIV-positive adults. Abacavir/dolutegravir/lamivudine is a first-line DHHS recommended regimen that can be used instead of TDF containing regimens in patients with underlying renal dysfunction or at high risk for renal effects [4]. In randomized controlled trials, treatment with abacavir/lamivudine resulted in significantly less BMD loss compared to TDF/FTC [9]. While treatment with abacavir has been proven to be safe and effective in HLA-B*5701-negative HIV-1 positive persons, DHHS guidelines recommend avoiding abacavir in patients with known high cardiovascular risk, such as hypertension, hypercholesterolemia and smoking, due to reports of an association between abacavir use and myocardial dysfunction [10-12]. In contrast, several studies reported no myocardial risk with abacavir use or no increased risk compared to those on a non-abacavir containing regimen [13-15]. Hence an overall consensus on the issue has not been reached.

For the management of HIV treatment-experienced patients being considered for a regimen switch, DHHS guidelines state that the fundamental principle of a regimen switch is to maintain viral suppression without jeopardizing future treatment options [4]. Regimen modification should be made cautiously because archived drug resistant viruses harbored within latently infected cells have the opportunity to emerge under appropriate selective drug pressure. Therefore, it is critical to review the full ARV treatment history of patients prior to selecting a new treatment regimen. HIV-1 DNA resistance testing may be used in combination with historical plasma RNA resistance testing to guide regimen switching in the setting of viral suppression [16]. This testing may

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also provide added information regarding archived drug resistance when prior resistance test results are unavailable or incomplete.

The goal of this sub-study was to determine if HIV-1 DNA resistance testing could successfully assess eligibility for a switch from a tenofovir-containing regimen (either TDF or TAF) to the fixed-dose combination (FDC) of abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) [17] to evaluate changes in bone mineral density among HIV-1 positive adults at least 50 years of age with virologic suppression.

Research Methodology

Study population

The HIV-1-infected individuals evaluated in this study were enrolled in the STRUCTR trial (ClinicalTrials.gov Identifier: NCT03275701). Briefly, STRUCTR is a 96-week, single-arm, single-center study to evaluate bone health in HIV-positive adults who switched from their ongoing suppressive regimen containing an integrase strand transfer inhibitor (INSTI) and either TDF or TAF as the backbone NRTI to the FDC INSTI-based study treatment of ABC/DTG/3TC. Screening assessments included an HIV-1 DNA resistance assay evaluation to assess pre-existing resistance to any of the study treatment components because virologic suppression precludes the use of standard resistance testing.

Enrollment eligibility required the following: Participants were at least 50 years of age and were on a stable antiretroviral FDC of either elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/c/FTC/TAF) [18] or elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/c/FTC/TDF) [19] for ≥3 months preceding screening. Viral suppression, defined as plasma HIV-1 RNA <50 copies/mL for ≥3 months preceding screening and plasma HIV-1 RNA <50 copies/mL at the screening assessment, was required in addition to documentation of a negative human leukocyte antigen (HLA)-B*5701 allele assessment to minimize the risk of abacavir hypersensitivity. Participants were excluded from the study if they had documented resistance to any component of the study treatment identified by HIV-1 DNA resistance testing at screening. Regimen switches were made when the study subject's virus was identified as sensitive to each component of the ABC/DTG/3TC regimen. This was done to remove the potential impact that mutations could have on maintaining viral suppression, especially in those patients with multiple thymidine analog mutations and/or M184V. Among those participants who switched regimens, viral load measurements were obtained per study protocol through weeks 24 and 48 using the Roche TaqMan 2.0 assay (Roche Diagnostics, Rotkreuz, Switzerland). The viral suppression rate was calculated with a 95% confidence interval using the binomial Clopper-Pearson exact statistical analysis method.

Drug susceptibility assessments

Susceptibility to ABC/DTG/3TC was assessed using an HIV-1 DNA genotypic resistance assay (GenoSure Archive®, Monogram Biosciences, South San Francisco, CA). In this assay, genomic DNA is extracted from EDTA whole blood specimens followed by triplicate nested PCR amplification of the HIV pol region. The resulting amplicons are pooled, purified and prepared for libraries using Nextera XT library and index kits, followed by 2 × 150 base paired-end sequencing on the Illumina MiSeq platform. Resulting FASTQ files are processed through a custom bioinformatics analysis pipeline. Briefly, reads are quality trimmed, then overlapping paired-end reads are joined and aligned to a reference sequence (NL43 GenBank: KM390026.1) in a codon-aware manner. Alignments are checked to determine minimal quality metrics: coverage >1000× at all positions, >Q30 average phred score at all positions. Aligned reads are individually evaluated for evidence of APOBEC3G/3F induced G to A hypermutation using a naïve Bayes classification model. The frequency of each variant is calculated after excluding reads that are classified as hypermutated. Although NGS platforms allow determination of variants at very low levels, reporting thresholds are set to 10% to minimize the impact of false positives secondary to APOBEC hypermutation-induced variants. Non-APOBEC drug resistance mutations are reported at a threshold of 3%.

Results

Study screening and baseline characteristics

Seventy-two participants were screened and fifty were enrolled in the study (31% screen failure rate) (Table 1). The most common cause for screen failure was predicted resistance to one or more components of the study drugs (12.5%). Six participants were resistant to both abacavir and lamivudine, two participants were resistant to abacavir only and one participant was resistant to lamivudine only. Substitutions at positions 41, 67, 184 and 215 in reverse transcriptase were most common. There was one reported substitution in

Table 1. Reasons for screen failure.

Reason	Number of screen failures
Resistance to abacavir and lamivudine	6
Resistance to abacavir only	2
Resistance to lamivudine only	1
Non-reportable HIV-1 DNA resistance results	3
HLA-B*5701 positive	2
Consent withdrawal	1
Lost to follow-up	3
HBV infection	1
Site error	3
Screen failures due to drug resistance mutations	
Patient ID	**Drug resistance mutations detected**
1	RT: M41M/L, D67D/N, V118V/I, M184M/V, L210L/W, T215T/Y
2	RT: L74L/V, M184M/V
3	RT: D67D/N, V75V/L, M184M/V, K219K/C
4	RT: M41M/I/L, T215T/N/S/Y
5	RT: M41L, L210W
6	RT: M41M/L, E44E/D, D67D/N, M184M/V, T215T/Y
7	RT: M41L, E44E/D, D67D/N, V75V/A, V118V/I, M184M/V, L210W, T215Y, K219K/N
8	RT: M41M/L, D67D/N, K70K/R, M184M/V, T215T/N/S/Y, K219K/Q
9	IN: S147S/G *Not randomized in error
10	RT: M184M/V

RT: Reverse Transcriptase; IN: Integrase

integrase (S147S/G), which confers resistance to elvitegravir. This substitution did not exclude the participant from the study. However, in error, this participant was not randomized. HIV DNA resistance data was not obtained for three participants due to non-reportable assay results (4% failure rate). Two participants were excluded based on HLA-B*5701 test results. Additional screen failures included consent withdrawal, loss to follow-up, HBV infection and site error.

Baseline characteristics of the participants enrolled in this study are shown in Table 2. All virologically suppressed participants enrolled in the study were male and at least 50 years of age who had been on at least one other ARV regimen prior to their regimen at screening. Participants were prescribed EVG/c/FTC/TAF (86%) or EVG/c /FTC/TDF (14%) and had a mean CD4 cell count of 709 cells/mm^3 at the time of screening. The mean time from seroconversion was ≥14 years and the majority of participants were Caucasian (82%).

Study outcome

The proportion of study participants that maintained viral suppression (<50 copies/mL) at weeks 24 and 48 as determined by quantitative plasma HIV-1 RNA were evaluated. At week 24, 44 of 44 study participants were virologically suppressed (HIV RNA <50 copies/mL, 95% CI [0.920, 1]). At week 48, 41 of 42 participants were virologically suppressed (HIV RNA <50 copies/mL, 95% CI [0.874, 0.999]); 1 participant had a viral load of 62 copies/mL (Figure 1). Eight of 50 enrolled participants discontinued the study. Four participants discontinued due to adverse events including diarrhea, nausea, headache, insomnia, anxiety and elevated ALT/AST thought to be related to study medications. Two participants were lost to follow-up. One participant withdrew consent and one participant had missing viral load data at week 48.

Discussion

HIV infects long-lived cells that can harbor integrated copies of the proviral genome. These viral genomes represent wild-type as well as mutated viral strains, archived during primary infection and throughout ARV treatment [20]. When activated from latency, these cells can serve as a source of drug-resistant infectious virus. An HIV-1 DNA genotype uses the archived proviral DNA as a resource to provide historical resistance information which cannot be captured in the plasma RNA since plasma virus represents the most current form of the virus produced from actively replicating cells.

The importance of establishing pre-existing resistance prior to ARV treatment modification was highlighted in the SWITCHMRK studies, which demonstrated that patients may harbor drug resistant variants that can emerge when a suboptimal switch regimen is selected [21]. In these studies, historical resistance was not documented at baseline, and baseline resistance testing could not be performed because participants were required to have an undetectable viral load at screening. Genotypic resistance testing at the time of failure identified the presence of resistance mutations to the switch regimen. These findings suggested that the higher failure rate in the switch regimen group was likely due to a treatment backbone that was not fully active, thereby facilitating virologic breakthrough. A similar example of treatment failure due to unknown pre-existing resistance was demonstrated in a subgroup analysis of the SPIRIT study [22]. In this study, although HIV-1 RNA resistance history was documented before a regimen switch was made, post hoc analysis of PBMCs collected at study baseline showed that a patient who ultimately experienced virologic failure would have been excluded from the study due to pre-existing mutations conferring resistance to an ARV in the switch regimen. The use of an HIV-1 DNA genotype as part of the screening process in switch studies may have the potential to prevent these types of study enrollment errors. The clinical utility of HIV-1 DNA genotype data has also been demonstrated in two small studies where HIV-1 DNA resistance information was used to successfully guide treatment regimen switches [23,24] resulting in reduced pill burden and dosing frequency [24].

All available background information including historical resistance tests and treatment outcomes should be considered before modification of a suppressive antiretroviral regimen. HIV-1 DNA genotyping is evolving as a very useful tool to help guide therapy adjustment and identify the potential for treatment failure especially when historical data is unavailable. Therefore, the reliability of DNA resistance data to accurately predict resistance is important. In some studies, HIV-1 DNA resistance testing has been shown to have good concordance (89%-91%) with plasma RNA resistance [23-25]. Additionally, mutations in the HIV-1 DNA genotype may be detected when not identified in the historical plasma RNA genotype [26,27]. However, other studies reported a higher discordance [27-30] when comparing HIV-1 DNA resistance testing to RNA resistance testing. While the reason for these differences is still unclear, possible explanations may include: 1) differences in sequencing methodology (conventional Sanger vs next generation sequencing), 2) sampling bias due to limited HIV copy number in PBMC DNA (≤100 copies/mL) [25], 3) the PBMC

Table 2. Baseline characteristics (n = 50).

Characteristics	Mean (range) or Percent
Age	54.6 (50-72)
Male	100%
Race/Ethnicity	
White	82%
Black	4%
Hispanic	6%
Unspecified	8%
Regimen at time of screening	
EVG/c/FTC/TAF	86%
EVG/c/FTC/TDF	14%
At least 1 therapy switch	100%
Time since seroconversion (years)	14.2 (3-33)
1-10 years	44%
11-20 years	38%
>20 years	18%
Baseline HIV-1 RNA <50 copies/mL	100%
Screening mean CD4 (cells/mm^3)	709
Week 24 mean CD4 (cells/mm^3)	711
Week 48 mean CD4 (cells/mm^3)	739

EVG/c/FTC/TDF: Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate

EVG/c/FTC/TAF: Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide

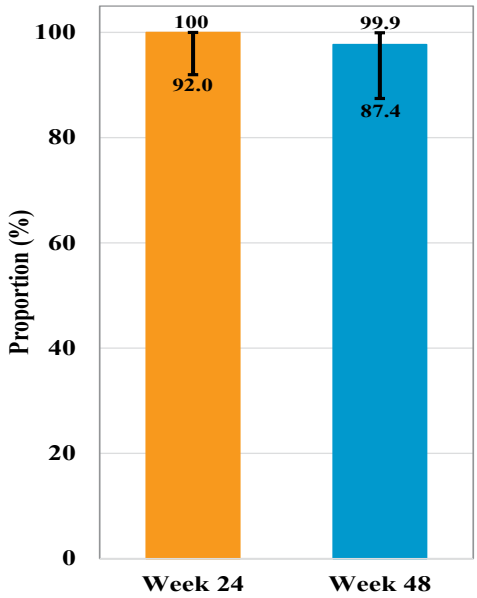

Figure 1. Proportion of patients with successful viral suppression at week 24 and week 48 after regimen switch. 95% confidence interval for the proportion with lower and upper bound is shown on the graph.

compartment represents only one source of latently infected cells, and 4) the impact of viral reservoir dynamics as it relates to viral and cell proliferation and turnover of latently infected cells [31,32]. Other factors such as the viral load at the time of failure, the time to virologic suppression, the duration of suppression, and the CD4 cell count may all play a role.

The main limitations of our study are the lack of a control group, small sample size and lack of gender diversity. An additional limitation is the exclusion of patients harboring M184V or other NRTI resistance mutations which ultimately might not have impacted virologic suppression. Aside from older age, the study participants did not meet the criteria for a high risk group which would preclude the use of abacavir. No cardiovascular events were reported after 48 weeks of follow up.

Conclusion

In this pre-selected patient population, HIV-1 DNA resistance testing successfully identified candidates for ARV treatment modification to an alternative single tablet regimen. In virologically suppressed patients, HIV-1 DNA resistance testing provided archived resistance information by extracting and sequencing cell-associated DNA in latently infected cells. These successful regimen switches, based solely on information provided by the HIV-1 DNA resistance assay, demonstrate the reliability of the assay when used as the only resource for HIV-1 drug resistance information prior to a regimen switch. Additional studies utilizing HIV-1 DNA resistance testing to prospectively assess virologic outcomes in real-world clinic populations is warranted.

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