Eight-day Inpatient Directly Observed Therapy for Antiretroviral Therapy (ART) Failure: A Tool For Preventing Unnecessary ART Changes and Optimizing Adherence Support

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Eight-day inpatient directly observed therapy confirmed nonadherence as the major cause of virologic failure for 9 (45%) of 20 highly treatment-experienced persons with human immunodeficiency virus, extensive antiretroviral drug resistance, and high self-reported adherence rates, preventing unnecessary regimen changes.

Keywords. antiretroviral therapy; viral failure; adherence; directly observed therapy; drug resistance.

With effective antiretroviral (ARV) therapy (ART), >85% of persons with human immunodeficiency virus (HIV) (PWH) are able to achieve viral suppression [1], leading to drastic reductions in HIV-related mortality and morbidity rates [2, 3]. However, there remains a subgroup of PWH who have intermittent or persistent viremia despite being prescribed ART [1]. Management of these patients can be challenging and resource intensive. Inconsistent adherence, suboptimal ART potency, and drug resistance are among the factors contributing to virologic failure [4]. When suboptimal adherence is the primary reason for persistent viremia, frequent regimen changes without addressing adherence barriers can cause further accumulation of drug resistance mutations (DRMs), limiting future treatment options. However, in these patients with viremia, drug resistance, and uncertain adherence levels, assessing the efficacy of ART regimens in the outpatient setting

can be difficult. In our prior experience, several patients who were hospitalized for acute illnesses had substantial declines in viral load (VL) after daily ARV administration by nursing staff. Our study enrolled PWH with documented virologic failure and used an 8-day inpatient directly observed therapy (DOT) to assess the virologic efficacy of the participants' ART regimens.

METHODS

PWH were eligible if they had virologic failure (defined by ≥ 2 most recent plasma HIV VLs >1000 copies/mL), despite ≥ 2 ART regimens, while receiving the current regimen for >6 months. The current study (NCT01976715) was approved by the Institutional Review Board of the National Cancer Institute. All participants provided written informed consent.

Before study enrollment, outside medical records were reviewed for ART history, treatment responses, and prior resistance test results. After screening and baseline visits confirming a VL >1000 copies/mL, participants were admitted to the National Institutes of Health Clinical Center for an 8-day inpatient DOT that was self-guided; participants requested their ARV drugs within 2 hours before or after the times mimicking their home routine. If they failed to request by 2 hours after the scheduled time, doses were administered and recorded accordingly. VL was measured on day 1 before DOT and on days 3, 5, and 8 of DOT. The trough concentration of 1 selected ART drug was measured before the first administered dose, then repeated 2–3 hours later to assess the adequacy of oral absorption. A repeat trough concentration was obtained on day 8. In-house genotypic resistance testing (Supplementary Material) was performed on day 1 and repeated on day 8 if the VL remained >500 copies/mL. HIV/ART education, adherence counseling, and psychosocial assessment and support were provided by medical, nursing, pharmacy, and social work staff during DOT and made available at all follow-up visits. After DOT, participants returned for outpatient follow-up visits at 2, 4, 8, and 12 weeks then every 12 weeks thereafter for 24 months.

Data Analysis

The DOT response was measured as the VL change from screening to DOT day 8, to account for VL decline due to improved adherence between study enrollment and DOT. Based on Food and Drug Administration guidance for ART-experienced patients with drug resistance [5], individuals were classified as DOT responders (DOT-Rs) if they had a VL decline $>0.5 \log_{10}$ copies/mL from screening to DOT day 8, and as DOT nonresponders (DOT-NRs) if the VL decline was $\leq 0.5 \log_{10}$ copies/mL.

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The 2017 International AIDS Society–USA mutation list [6] and Stanford HIV Drug Resistance Database algorithm [7] were used to calculate genotypic susceptibility scores (GSSs) of the regimens [8] (Supplementary Table 1). Demographic, virologic, and immunologic parameters were compared between DOT-Rs and DOT-NRs using a 2-sample *t* test for normally distributed continuous variables, the Mann-Whitney *U* test for variables that were not normally distributed, and the Boschloo test for binary variables. Owing to multiple comparisons, *P* values <.05 and <.01 were considered suggestive and stronger evidence, respectively. A sensitivity analysis was conducted using the more sophisticated multiplicity adjustment method of Westfall [9].

RESULTS

Of 25 PWH screened for the study, 23 met eligibility criteria and were enrolled (Supplementary Figure 1). This report focuses on the 20 participants who completed an 8-day inpatient DOT (Table 1). Their median age was 45.5 years, 60% were male, 85% were black, and 25% had acquired HIV perinatally. Most participants had advanced HIV infection, with a median CD4 cell count of 54.0/μL, and 90% had a CD4 cell count <200/μL. The median screening VL was 4.46 log₁₀ copies/mL. These participants were highly ART experienced, with a mean ART duration of 17.2 years (standard error, 6.1 years), a mean of 11.8 (4.5) prior ART drugs, and a median of 20.5 DRMs from the International AIDS Society–USA mutation list [6]. Five (25.0%) received 1 or 2 nucleoside reverse-transcriptase inhibitors as their initial ART regimen. The median GSS of the ART regimen at enrollment was 1.0 (interquartile range, 0.1–2.0).

Nine (45%) participants were DOT-Rs, with a decline in plasma VL >0.5 log₁₀ copies/mL during their pre-enrollment ART regimens. This includes 4 of 5 participants (80%) who acquired HIV perinatally. The median HIV RNA changes from screening to day 8 for DOT-Rs and DOT-NRs were –1.52 and –0.10 log₁₀ copies/mL, respectively (Supplementary Figure 2). During inpatient DOT, 3 of 9 DOT-Rs (33.3%) and 5 of 11 DOT-NRs (45.5%) did not request ≥1 of their ART doses. Compared with DOT-NRs, DOT-Rs had fewer prior ARVs (mean, 8.8 vs 14.3; *P* = .004), fewer DRMs across 4 drug classes (median, 6.0 vs 24.0; *P* = .001), higher GSSs (median, 2.0 vs 0.1; *P* < .001), and less formal education (44.4% vs 90.9% with more than a high school education; *P* = .03), although this latter comparison did not meet the more stringent a level of .01 (Table 1). Drug concentration results are reported in Supplementary Table 2. Very similar conclusions were reached using Westfall's multiplicity adjustment methods [9].

Six of 9 DOT-Rs had ≥6 months of follow-up. Five of 6 (83.3%) achieved VL <40 copies/mL at ≥1 outpatient follow-up visits, and only 1 of 6 (16.7%) maintained virologic suppression for ≥6 months. However, all 6 had gains in CD4 cell count, with a median increase of 60/μL (interquartile range, 23–94/μL)

between screening and 6 months after screening, compared with a median decline in CD4 cell count of 30/μL during the 6 months before study. Eight DOT-NRs had active ART options and returned for a second inpatient DOT to initiate a new regimen. Three participants had emergent DRMs during study, and 1 switched from R5 to dual/mixed tropic virus.

DISCUSSION

Our study participants were highly ART experienced with low CD4 cell counts, extensive multiple-class drug resistance, and limited ARV drug options. Review of their medical records revealed long histories of suboptimal adherence or treatment interruptions and disengagement in care. Although these individuals represent a minority of PWH currently in care, they are at the highest risk of disease progression and pose considerable management challenges. Inpatient DOT identified 45% of participants who had a VL decline of >0.5 log₁₀ copies/mL with their “failing” regimen, confirming nonadherence as a major cause of virologic failure and preventing unnecessary regimen changes.

Five of the 6 DOT-Rs with >6 months of follow-up were able to achieve a VL <40 copies/mL at ≥1 follow-up visits. The inpatient setting provided the multidisciplinary team more time to identify and address key adherence barriers. Sharing VL results with DOT-Rs during and after completion of DOT was also a powerful tool to reinforce the efficacy of their ART regimens and to motivate participants to continuous adherence after discharge. However, although adherence improved during and immediately after DOT, the majority of DOT-Rs experienced viral rebound after DOT, reflecting the difficulty for these individuals of maintaining optimal adherence as outpatients. In selected cases, a strategy to deescalate from inpatient DOT to some form of outpatient DOT may further improve adherence. Despite not being able to maintain viral suppression, all 6 DOT-Rs who had 6 months of follow-up had gains in CD4 cell counts.

Management of patients with multiple-class drug resistance requires additional resources with more frequent clinic visits and laboratory follow-up and more case management, and it often requires expert consultation to design more complex and costly ARV regimens. We observed more socioeconomic barriers among the participants identified as having nonadherence-driven virologic failure (DOT-Rs) than among the DOT-NRs. Most notably, the DOT-Rs had lower education levels and required more frequent social work assistance for employment and housing instability, food insecurity, and mental health conditions. Individuals who share these characteristics with DOT-Rs may be an important group for early targeted adherence interventions to preserve future treatment options.

Even though inpatient DOT is impractical in most clinical settings, less resource-intensive outpatient strategies might be of value. Virtual DOT using smart phones or other video enabled devices has been successful in monitoring medication

Table 1. Baseline Characteristics, Directly Observed Therapy (DOT) Results, and Treatment Outcomes in Study Participants, Overall and by DOT Treatment Response

Characteristic, Result, or Outcome	Participants, No. (%) ^a			PValue ^b
	Overall (N = 20)	DOT1-Rs (n = 9)	DOT1-NRs (n = 11)	
Demographics				
Age, median (IQR), y	45.5 (26.0–51.3)	26.0 (24.0–47.0)	49.0 (42.5–51.5)	.09
Male sex	12 (60.0)	4 (44.4)	8 (72.7)	.26
Black race	17 (85.0)	8 (88.9)	9 (81.2)	>.99
Post-high school education	14 (70.0)	4 (44.4)	10 (90.9)	.03
Unemployed	7 (35.0)	5 (55.6)	2 (18.2)	.12
Housing instability	5 (25.0)	5 (55.6)	0 (0.0)	.005
Food insecurity	3 (15.0)	3 (33.3)	0 (0.0)	.052
Mental health concerns	8 (40.04)	6 (66.7)	2 (18.2)	.06
Current alcohol use	10 (50.0)	4 (44.4)	6 (54.5)	>.99
Illicit drug use	6 (30.0)	3 (33.3)	3 (27.3)	>.99
Previous drug use	11 (55.0)	6 (66.7)	5 (45.5)	.38
HIV risk factor				
MSM	8 (40.0)	2 (22.2)	6 (54.5)	.16
Heterosexual	7 (35.0)	3 (33.3)	4 (36.4)	
Perinatal	5 (25.0)	4 (44.4)	1 (9.1)	
Screening results				
VL, median (IQR), log ₁₀ copies/mL	4.46 (4.32–5.00)	4.35 (4.17–4.51)	4.64 (4.36–5.00)	.33
CD4 cell count, median (IQR), cells/μL	54.0 (13.8–90.3)	66.0 (26.0–89.0)	50.0 (10.5–82.0)	.57
CD4 cell count <200/μL	18 (90.0)	9 (100.0)	9 (81.2)	.38
ART experience and resistance				
Time since diagnosis, mean (SE), y	21.3 (7.0)	20.7 (7.4)	21.8 (7.0)	.72
Time on ART, mean (SE), y	17.2 (6.1)	14.2 (6.1)	19.6 (5.2)	.047
No. of ART drugs, mean (SE)	11.8 (4.5)	8.8 (3.7)	14.3 (3.6)	.004
Prior mono- or dual-NRTI therapy	5 (25.0)	1 (11.1)	4 (36.4)	.22
Prior T-20 or maraviroc salvage therapy	6 (30.0)	1 (11.1)	5 (45.5)	.10
Total no. of major and minor DRMs by ARV drug class, median (IQR) ^c	14 (5.0–18.0)	5.0 (3.0–7.0)	18.0 (14.5–19.0)	<.001
Total no. of DRMs by ARV drug class, median (IQR)	20.5 (7.5–24.0)	6.0 (5.0–12.0)	24.0 (21.5–25.5)	.001
NRTI DRMs	4.5 (1.0–7.0)	1.0 (1.0–2.0)	6.0 (5.0–7.0)	.003
NNRTI DRMs	3.0 (1.8–4.0)	2.0 (1.0–3.0)	4.0 (3.0–5.0)	.016
PI DRMs	9.0 (3.0–12.3)	3.0 (2.0–6.0)	11.0 (10.0–14.0)	.001
INSTI DRMs	1.0 (0.0–3.0)	0.0 (0.0–0.0)	3.0 (1.5–3.0)	.002
GSS, ^d median (IQR)	1.0 (0.1–2.0)	2.0 (2.0–2.6)	0.1 (0.0–0.3)	<.001
ART daily pill burden, median (IQR)	3.5 (2.0–5.0)	3.0 (2.0–5.0)	4.0 (2.5–5.5)	.24
Total daily pill burden, median (IQR)	10.0 (6.0–12.0)	7.0 (5.8–11.5)	10.0 (9.3–11.8)	.49
DOT results				
VL change from screening to DOT d 8, median (IQR), log ₁₀ copies/mL	–0.22 (–1.51 to –0.08)	–1.52 (–1.47 to –1.96)	–0.10 (–0.09 to 0.14)	<.001
Participants who requested <100% of DOT ART doses	8 (40.0)	3 (33.3)	5 (45.5)	.60
Post-DOT treatment outcomes, for participants with ≥6-mo follow-up				
	(n=17)	(n=6)	(n=10)	
VL <40 copies/mL achieved (with >6-mo follow-up) at ≥1 study time point	11 (64.7)	5 (83.3)	6 (60.0) ^e	.42
Maintained VL <40 copies/mL for 6 mo (>6-mo follow-up)	5 (29.4)	1 (16.7)	3 (30.0)	>.99
CD4 cell count increased between screening and 6 mo later	13/16 (81.3)	6 (100.0)	7 (70.0)	.16

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; DOT, directly observed therapy; DOT-NRs, DOT nonresponders; DOT-Rs, DOT responders; DRMs, drug resistance mutations; GSS, genotypic susceptibility score; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; IQR, interquartile ratio; MSM, men who have sex with men; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; SE, standard error; T-20, enfuvirtide; VL, viral load.

^aData represent no. (%) of participants unless otherwise specified.

^bDOT-R and DOT-NR parameters were compared by means of 2-sample *t* test for normally distributed continuous variables, Mann-Whitney *U* test for variables that were not normally distributed, and Boschloo's test for binary variables.

^cAccording to the 2017 International AIDS Society–USA mutation list [6].

^dGSSs range from 0 (no ARV agents with activity) to 3 (3 fully active ARV agents in regimen).

^eEight DOT-NRs switched to optimized ARV regimens after the first DOT. The virologic responses reflect response while on the new optimized ARV regimen.

adherence for latent and active tuberculosis treatment [10, 11] and could also be an effective tool for assessing failing ART regimens. Finally, early targeted interventions to promote

adherence [12], including long-acting injectable or implantable ARVs, are needed to maintain treatment options for individuals at high risk of virologic failure.

Owing to the success of current ART, enrollment in our study has been limited to a small number of individuals retained in care with virologic failure who are able to commit to an 8-day inpatient admission. Despite the small sample size, we showed that short-term DOT can be an effective tool for identifying suboptimal adherence as the major cause of virologic failure, preventing unnecessary regimen changes and guiding subsequent follow-up.

Supplementary Data

Supplementary materials are available at *Clinical 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.

Notes

Author contributions. H. C. L. and A. K. P. contributed to conception, design, and implementation of the study. Y. M. provided support in subject recruitment and maintenance of regulatory requirements for the study. N. E. W., N. D., E. L., S. S. K., P. S., and A. K. P. contributed to patient care and data collection. F. M. provided patient care guidance, data interpretation, and critical guidance in article drafting. R. D. performed genotypic testing on all participant samples and provided laboratory analysis and interpretation. N. E. W., S. S. K., and M. P. contributed to data analysis and interpretation. N. E. W. and A. K. P. drafted and revised the article. All authors critically reviewed the article and approved the final version.

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References

1. Nance RM, Delaney JAC, Simoni JM, et al. HIV viral suppression trends over time among HIV-infected patients receiving care in the United States, 1997 to 2015: a cohort study. *Ann Intern Med* **2018**; 169:376–84.
2. Low A, Gavrilidis G, Larke N, et al. Incidence of opportunistic infections and the impact of antiretroviral therapy among HIV-infected adults in low- and middle-income countries: a systematic review and meta-analysis. *Clin Infect Dis* **2016**; 62:1595–603.
3. Hanhoff N, Vu Q, Lang R, Gill MJ. Impact of three decades of antiretroviral therapy in a longitudinal population cohort study. *Antivir Ther* **2019**. doi:10.3851/IMP3287.
4. Panel on Antiretroviral Guidelines for Adults and Adolescents, Department of Health and Human Services. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Available at: <http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf>. Accessed 1 April 2019.
5. Food and Drug Administration. Human immunodeficiency virus-1 infection: developing antiretroviral drugs for treatment guidance for industry. **2015**. Available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM355128.pdf>. Accessed 1 April 2019.
6. Wensing AM, Calvez V, Günthard HF, et al. 2017 Update of the drug resistance mutations in HIV-1. *Top Antivir Med* **2017**; 24:132–3.
7. Liu TF, Shafer RW. Web resources for HIV type 1 genotypic-resistance test interpretation. *Clin Infect Dis* **2006**; 42:1608–18.
8. Anderson JA, Jiang H, Ding X, et al; AIDS Clinical Trials Group Study 359 Protocol Team. Genotypic susceptibility scores and HIV type 1 RNA responses in treatment-experienced subjects with HIV type 1 infection. *AIDS Res Hum Retroviruses* **2008**; 24:685–94.
9. Westfall PH. Resampling-based multiple testing. New York, NY: John Wiley & Sons, **1993**:32–75.
10. Lam CK, McGinnis Pilote K, Haque A, Burzynski J, Chuck C, Macaraig M. Using video technology to increase treatment completion for patients with latent tuberculosis infection on 3-month isoniazid and rifampentine: an implementation study. *J Med Internet Res* **2018**; 20:e287.
11. Story A, Garfein RS, Hayward A, et al. Monitoring therapy compliance of tuberculosis patients by using video-enabled electronic devices. *Emerg Infect Dis* **2016**; 22:538–40.
12. Kanfers S, Park JJ, Chan K, et al. Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. *Lancet HIV* **2017**; 4:e31–40.