



Improved Virologic Outcomes and Less HIV Resistance for HAART-Experienced Substance Users Receiving Modified Directly Observed Therapy (MDOT): Results from a Randomized Controlled Trial

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BACKGROUND

- Active substance users have demonstrated lower rates of adherence to HAART and less virologic benefit from treatment
- The goal of modified directly observed therapy (MDOT) for HIV in high risk communities is to increase medication adherence and decrease HIV-related morbidity and mortality through decreasing PVL and increasing CD4
- MDOT is also known as directly administered antiretroviral therapy (DAART), an alternative term that can be used synonymously

MDOT STUDY DESIGN

"We conducted a randomized controlled trial to evaluate, among current substance users on once-daily HAART, the effect of MDOT versus standard of care (SOC) on plasma HIV RNA and the development of antiretroviral resistance

- Participants had to have documented genotypic sensitivity to a once-daily HAART regimen
- Between 12/2001 and 6/2004, patients from Rhode Island and Southeastern Massachusetts clinics were referred by their primary care provider (PCP) because they were failing, or at high risk of failing, HAART therapy.
- Patients were screened via interviewer-administered questionnaire, viral load, and genotype

- Eligible participants were randomized to SOC or MDOT, stratified by HAART experience
- All participants were placed on a once-daily HAART regimen recommended by the study team and their PCP after considering genotype results, toxicity profiles, and prior HIV medications

- Participants in the MDOT arm filled prescriptions and gave HIV medications to the study nurse
- All MDOT participants kept a one-week supply of medications so that they could self-administer HIV medications if an outreach visit was missed
- An Outreach Worker (RW) delivered medications and observed doses at a location of the participant's choice

- Assessments included interviewer-administered questionnaires and viral load and CD4 testing at baseline, 1 month, 3 months, and every 3 months up to 1 year
- Follow up genotype testing was performed on participants who had ≤ 1 log drop in PVL on 2 consecutive viral load tests

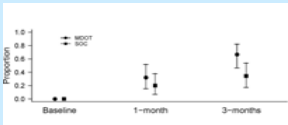
TESTING

- Viral Load Testing
 - AMPLICOR HIV-1 Monitor Test
 - Testing done using ultrasensitive protocol
- Resistance Testing
 - TruGene HIV-1 Genotyping Kit
 - OpenGene DNA Sequencing System

ANALYSIS: 3 MONTH ENDPOINTS

- CD4 and Plasma Viral Load (PVL)
 - Suppression: > 2 log drop in HIV RNA or PVL < 50 copies/ml
 - Treatment failure: ≤ 1 log drop in PVL on 2 consecutive viral load tests
- Genotypic Resistance
 - Resistance to at least one antiretroviral medication.
- MDOT was effective in HAART-experienced participants (80%) and did not provide any additional benefit over SOC in naive patients. Therefore, this analysis is restricted to HAART-experienced individuals

PVLSUPPRESSION BY TREATMENT ARM FOR HAART-EXPERIENCED PARTICIPANTS (> 2 LOG DROP IN PVL OR PVL <50 COPIES/ML)



A significantly higher proportion of MDOT participants achieved viral load suppression at 3 months compared with SOC (p<.05)

PVL BY MONTH FOR HAART-EXPERIENCED PARTICIPANTS



The median PVL was lower at 3 months in the MDOT arm as compared with SOC (p<.05)

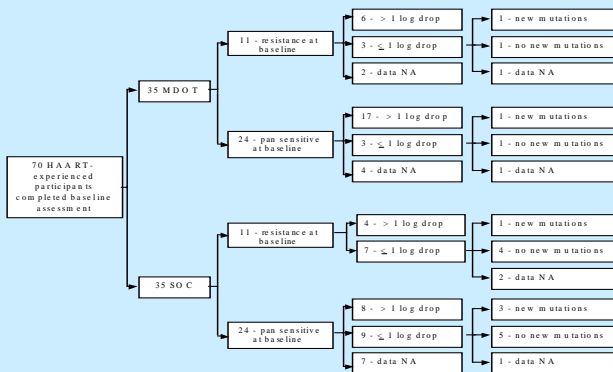
CD4 CHANGE AT 3 MONTHS BY TREATMENT ARM FOR HAART-EXPERIENCED PARTICIPANTS

Group	Median change in CD4 count (cells/mm ³)	Estimated mean CD4 count (95% CI) at 3 months (95% CI)	Treatment effect of MDOT over SOC (95% CI)
MDOT	96	232 (198, 269)	60 (16, 105)
SOC	36	172 (139, 207)	

DEMOGRAPHIC AND SUBSTANCE USE PROFILE OF HAART-EXPERIENCED PARTICIPANTS (N=70)

	All participants (N=70)	DOT (n=35)	SOC (n=35)
Age (median)	43	45	42
Gender			
Male	50 (71%)	22 (63%)	28 (80%)
Female	20 (29%)	13 (37%)	7 (20%)
Current Employment	7 (10%)	3 (9%)	4 (11%)
History of Incarceration	57 (81%)	30 (86%)	27 (77%)
History of Homelessness	53 (76%)	30 (86%)	23 (66%)
Recent heroin and/or cocaine use*	53 (76%)	29 (83%)	24 (69%)
Recent alcohol abuse*	32 (46%)	14 (40%)	18 (51%)
Recent street drug use and/or prescription drug abuse*	14 (20%)	9 (26%)	5 (14%)

* Categories are not mutually exclusive



INDIVIDUALS WITH ≤ 1 LOG DROP AND DEVELOPMENT OF NEW MUTATIONS

Group	Baseline CD4	Baseline PVL	Baseline Mutations*	Initial Regimen	3 Month New Mutations
MDOT	25	2.58(1.18)	RTG, Elvarex, Tenofovir	K102M, V179E	
MDOT	45	3.38(K103N, M184V)	dtl, RTV, SQV, Tenofovir	K66R	
SOC	14	4.88	dtl, Elvarex, Tenofovir	K100I, K103N, V108I, P228H	
SOC	14	3.4	RTG, dtl, RTV, SQV	V179D, M184V, Y188L	
SOC	186	4.78	RTG, dtl, Elvarex, Tenofovir	K103N	
SOC	193	4.81(S190A, T215Y)	RTG, RTV, SQV, Tenofovir	M41L, D67N	

*No relevant PI mutations detected

INDIVIDUALS WITH ≤ 1 LOG DROP WITHOUT DEVELOPMENT OF NEW MUTATIONS

Group	Baseline CD4	Baseline PVL	Baseline Mutations*	Initial Regimen
MDOT	35	3.03		dtl, dtl, RTV, SQV
MDOT	438	4.53(K103N)		dtl, dtl, RTV, SQV
SOC	4	4.47(188L)		Atazanavir, dtl, RTV, Tenofovir
SOC	34	4.58(A89G, K103N, Y181C)		dtl, RTV, SQV, Tenofovir
SOC	43	5.45		Atazanavir, dtl, RTV, Tenofovir
SOC	168	4.78		dtl, NVP, Tenofovir
SOC	178	5.08(M41L, L210W, T215S)		dtl, Atazanavir, dtl, RTV, Tenofovir
SOC	232	4.97(K103N)		dtl, Kaletra
SOC	265	5.88(V179D)		dtl, Atazanavir, dtl, RTV
SOC	457	4.48(K103N, P228H)		dtl, RTV, SQV, Tenofovir
SOC	460	4.4		dtl, RTV, SQV, Tenofovir

*No relevant PI mutations detected

CONCLUSIONS

- In an intent-to-treat analysis, **HAART-experienced patients with active substance use** who were referred by their PCP and randomized to receive MDOT:
 - Had better PVL suppression than those on SOC at 3 months (OR - 2.88; 1.19, 6.96)
 - Had greater increases in CD4 cell counts than those on SOC at 3 months by an average of 60 cells/mm³ (16, 106)

- Among 70 HAART-experienced patients, 6/35 on MDOT were known to have ≤ 1 log drop in PVL at 3 months compared with 16/35 on SOC
 - 2/6 on MDOT were known to have developed new resistance mutations
 - 4/16 on SOC were known to have developed new resistance mutations

- Failure among patients on SOC was most often due to poor adherence without the generation of new mutations (9/16)
- In HAART-experienced patients with a high prevalence of baseline genotypic resistance (22/70)
 - On the MDOT arm, 3/11 were known to have ≤ 1 log drop in PVL
 - On the SOC arm, 7/11 were known to have ≤ 1 log drop in PVL

- MDOT was successful in substance using patients who continued to confront homelessness, incarceration and hospitalization
- MDOT is optimal as a **short-term** adherence intervention (<3 months) in HAART-experienced substance using patients. Long-term MDOT (e.g., > 6 months) is not feasible for:
 - Individuals with significant social instability
 - Individuals who are doing well and do not want to continue MDOT due to inconvenience

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