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Directly Administered Antiretroviral Therapy (DAART) in Residential Treatment Facilities in New York City

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ABSTRACT (updated):

Background: Success of antiretroviral therapy (ART) for HIV-1 infection may require strict adherence, so there is interest in using DAART to improve response to HIV therapy.

Objectives: To quantify the amount of antiretroviral drugs taken in a setting of DAART, to describe associated virologic and immunologic outcomes, and to assess factors associated with treatment failure.

Methods: Review of charts of persons admitted to two residential AIDS treatment facilities in New York, January 1998-June 1999, with CDC-defined AIDS, an observation time $\geq$ 180 days, and on highly-active ART. DAART was defined as recorded dispensation of each antiretroviral dose. Treatment failure was defined as a >0.5 log increase in HIV-1 RNA level, HIV-1 RNA level $\geq$ 100,000 copies/ml, or a > 30% decline in CD4+ cell count.

Results: 148 persons (75% who had previously received ART) had a median CD4+ cell count of 88 cells/l, and a median HIV-1 RNA level of 15,591 copies/ml (<400 copies/ml in 22% of persons). Persons were prescribed ART for 52,646 (88%) of 60,017 person-days of observation. Of doses prescribed, 99% were taken. During follow-up: 95 persons (64%) achieved an HIV-1 RNA level < 400 at least once; 60 persons (42%) had treatment failure at least once. Overall, persons who had treatment failure were more likely to have interrupted treatment > 7 days (odds ratio 3.92; confidence limits, 1.84, 8.44; p=.0001). On multivariate analysis, interruption of treatment > 7 days increased risk of staying a failure for persons already in a state of treatment failure (p=.001), but did not increase risk of treatment failure for persons already in a state of treatment response.

Conclusions: Under DAART persons received 99% of prescribed antiretroviral doses. Despite this, in a population in which three-quarters had previously taken ART, HIV-1 RNA level never decreased to <400 copies/ml in one-third of persons and treatment failed at least once in almost half. For persons already experiencing treatment failure, treatment interruptions were associated with decreased likelihood of transitioning to response. These results suggest the practical level of response attainable in an ART-experienced population of persons with AIDS.

BACKGROUND:

- >95% adherence to antiretroviral therapy (ART) for HIV-1 infection may be needed for optimal response
- Directly observed therapy improves adherence and response to tuberculosis treatment, but has not been widely studied for HIV treatment
- DAART is routinely provided in some residential AIDS treatment facilities in New York
- These residential AIDS treatment facilities
  - Are reimbursed by state Medicaid/Medicare
  - Provide comprehensive medical and support services
  - Often treat persons with drug use and mental health problems and inadequate social support
  - Maintain daily records, including per-dose medication administration records, for each patient

OBJECTIVES:

- To quantify the amount of antiretroviral drugs taken in a setting of DAART
- To describe associated virologic, immunologic, and clinical outcomes
- To assess factors associated with treatment failure

METHODS:

- Data Collection: Retrospective chart review
- Eligibility Criteria: Persons in two residential AIDS treatment facilities in New York City
  - admitted January 1998 June 1999
  - with an observation time $\geq$ 180 days
  - with CDC-defined AIDS
  - receiving highly-active ART
- Definitions:
  - DAART = recorded dispensation of each antiretroviral dose
  - ART Experience: Naïve = no prior ART
    Class-spared= Prior ART, inexperienced with either PIs or NNRTIs
    Not class-spared= Prior ART, experienced with both PIs and NNRTIs
  - Treatment failure = > 0.5 log increase from baseline in HIV-1 RNA level,
    or HIV-1 RNA level $\geq$ 100,000 copies/ml,
    or >30 % decline in CD4+ cell count
- Statistical Analysis: the Multi-State (semi-Markov) Model:
  (Anderson PK, Esbjerg S, Sorensen TI. Multi-state models for bleeding episodes and mortality in liver cirrhosis. Statist Med 2000; 19:587-599.)
  - We used the semi-Markov model to test the relationship between covariates for adherence, treatment interruption, and prior ART experience on transition rates between two states of HIV disease.
  - States for this model are "treatment failure" (defined above) compared to "treatment response" (all others).
  - Baseline state was categorized as "failure" for all ART-experienced persons with HIV-1 RNA level >100,000. Baseline state was categorized as "response" for all others.

RESULTS:

Preliminary Analysis

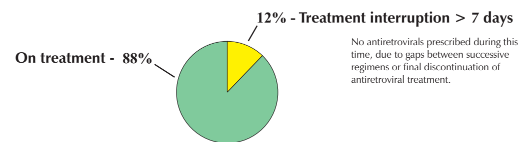
STUDY POPULATION

n = 148

	n=148
Median Age —years (range)	45 (21 -76)
Gender: **Male**	**114 (77%)**
Female	34 (23%)
Race/ethnicity: **Black, non-Hispanic**	**90 (61%)**
Hispanic	42 (28%)
White, non -Hispanic	15 (10%)
Risk for HIV: **Injection drug use**	**98 (66%)**
Heterosexual	25 (17%)
Male -male sex	9 (6%)
Unknown	15 (10%)
Past ART experience:	
Naïve	27 (18%)
Class-spared	**91 (61%)**
Not class-spared	**21 (14%)**
Unknown	9 (6%)
Baseline Values:	
Median HIV-1 RNA level (copies/ml)	15,591
HIV-1 RNA level < 400 copies/ml	32 (22%)
Median CD4+ cell count (cells/μl)	88

OBSERVATION TIME

total = 60,017 person days, median = 366 days per person



ADHERENCE

during time on treatment, # doses taken / # doses prescribed

- Overall: **99.0%** (329,439 doses taken / 332,910 doses prescribed)
- Specific: NRTIs: 99.1% (172,588 / 174,173)
  NNRTIs: 99.1% (34,521 / 34,841)
  PIs: 98.7% (118,524 / 120,043)

VIROLOGIC AND IMMUNOLOGIC OUTCOMES

- **HIV-1 RNA level < 400 copies/ml**, at least once during follow up: **95 persons (64%)**
- **Treatment failure**, at least once during follow up: **60 persons (42%)**

FACTORS ASSOCIATED WITH TREATMENT FAILURE (univariate)

- On univariate analysis, baseline CD4+ cell count, viral load, past ART experience not significantly associated with treatment failure
- **Persons with treatment failure were more likely to have interrupted therapy > 7 days**

	Treatment Failure, **EVER** n=60	Treatment Failure, **NEVER** n=88	Odds Ratio (confidence limits)	p-value
Interrupted ART > 7 days	**34**	**22**	**3.92 (1.84, 8.44)**	**0.0001**
Baseline CD4+ cell count, median (range), cells/μl	80.5 (3-834)	111 (1-625)		ns
Baseline HIV-1 RNA level, copies/ml	38, 767	12,000		ns
ART experience:				
Naïve	9 (15%)	18 (20%)	.69 (.26, 1.78)	0.53
Class-spared	34 (57%)	57 (65%)	.71 (.34, 1.47)	0.41
Not class-spared	12 (20%)	9 (10%)	2.19 (.88, 4.35)	0.15
Unknown	5 (8%)	4 (5%)	1.91 (.42, 8.94)	0.48

p-values determined by X^2, Fisher Exact, or Wilcoxon Rank Sum analysis

CLINICAL OUTCOMES

- HIV-associated illnesses:
  - 53 persons (36%), with 81 episodes of illness
  - 22 persons (15%) hospitalized for HIV-associated illnesses
- Hospitalizations:
  - 44 persons (30%) with 89 hospitalizations
  - 33 hospitalizations (37%) HIV-related
- Deaths/final discharge to hospital:
  - 23 persons (16%)

Multi-State (Semi-Markov) Model Analysis (multivariate)

TRANSITION FROM TREATMENT **FAILURE** TO TREATMENT **RESPONSE**:

85 intervals **in FAILURE** state, representing 10,875 days of observation, with 50 **transitions to RESPONSE**

Covariates	Risk (likelihood) of Transition to Response	p-value
ART Experience: Naïve	1.0 (Referent)	----
Class-spared	**.20**	**0.008**
Not class-spared	**.33**	**0.04**
Unknown	.59	0.45
% non-adherent days:	.94	0.22
Treatment interruption > 7days: No	1.0 (referent)	----
Yes	**.29**	**0.001**

- Persons with ART experience (class-spared or not class-spared) were less likely to transition to response.
- **For persons in treatment failure state, those with treatment interruption >7 days were less likely to transition to response.**

TRANSITION FROM TREATMENT **RESPONSE** TO TREATMENT **FAILURE**:

173 intervals **in RESPONSE** state, representing 32,937 days of observation, with 62 **transitions to FAILURE**

Covariates	Risk of Transition to Failure	p-value
ART Experience: Naïve	1.0 (referent)	----
Class-spared	1.65	0.19
Not class-spared	**2.38**	**0.05**
Unknown	2.75	0.02
% non-adherent days: (# days with imperfect adherence / # days during interval for which ART was prescribed)	**1.05**	**0.01**
Treatment interruption > 7days: No	1.0 (referent)	----
Yes	.70	0.19

- Persons with ART-experience (not class-spared) were more likely to transition to failure.
- Decreasing adherence was associated with increasing risk of transition to failure.
- **For persons in the treatment response state, treatment interruptions did NOT increase the risk of transitioning to failure.**

LIMITATIONS:

- OBSERVATIONAL DATA--number of outcome measures and intervals between outcome measures vary widely among persons.

The Multiple states (semi-Markov) model attempts to address this by making the transition between treatment response and treatment failure the unit of analysis, rather than the absolute "time to" an event.

- MEASURE OF ADHERENCE--it is possible that some doses dispensed were not actually taken, as it was not required that patients be observed ingesting the antiretroviral medication.

However, patterns of missed doses were consistent with accurate recording of doses not ingested: sporadic missed doses were commonly observed; consistently missed doses were addressed by an intervention (e.g. alteration of regimen for side effects), usually within 2-3 days.

- RESISTANCE TESTS NOT AVAILABLE.
- GENERALIZABILITY--includes only persons with advanced disease, who received these interventions for reasons other than non-adherence.

CONCLUSIONS AND DISCUSSION:

In a population of persons with AIDS, 3/4 of whom had previously taken ART, in residential treatment facilities in New York:

- **DAART resulted in 99% adherence.**
- **Under DAART:**
  - **2/3 of persons achieved an HIV-1 RNA level < 400 copies/ml at least once,**

    BUT

  - **almost 1/2 had treatment failure at least once.**

  These data suggest the (maximum) practical level of response attainable in an ART-experienced population of persons with AIDS.

While clinical trials with persons naïve to ART report response rates of 80-90%, cohort studies of inner-city outpatients, naïve to protease inhibitors, report response rates of only 37-42% (GM Lucas, Ann Intern Med. 1999; 131:81-87). Moreover, trials of salvage therapy report response rates of 30% for persons experienced with PIs and 15% for persons experienced with NNRTIs as well (J Mellors, Lancet 2000; 355:1435). So, in this population of persons with AIDS in which 75% had prior ART experience, that 64% achieved HIV-1 RNA level<400 copies/ml is favorable.

- **Treatment interruption > 7 days:**
  - **increased the risk of remaining a failure (decreased likelihood of transitioning to response) for persons already in a state of treatment failure,**

    BUT

  - **did NOT increase risk of treatment failure for persons already in a state of treatment response.**