



Measures of adherence to anti-retroviral therapy (ART) in DART Trial subjects, and their association with baseline characteristics and undetectable viral load

DART - Development of Antiretroviral Therapy in Africa



Background



- Few studies in Africa have attempted to describe adherence measures over one year.
- Good adherence is essential for successful ART provision, but simple measures have rarely been assessed or validated in African populations.
- Information regarding reasons for interrupting ART may lead to changes in disease management or identify priority areas for interventions.



Objectives



- To describe adherence in the first 12 months of DART.
- To investigate the relationship between change in viral load / viral suppression and adherence
- To assess ability of simple questions to identify good adherence
- To identify predictors of adherence.



Design



- The DART trial is an open-label, multi-centre, randomized trial, comparing two treatment monitoring strategies, two sites in Uganda and one site in Zimbabwe.

- Eligible subjects were
 - ✓ ART-naive
 - ✓ aged at least 18 years
 - ✓ with documented advanced HIV infection
 - ✓ WHO clinical stage 2, 3 or 4.
 - ✓ CD4 count of less than 200 cells/ml.

- Initially all participants given triple drug therapy with co-formulated ZDV/3TC (Combivir) with either TDF, NVP or ABC



Patient selection and data collection



At recruitment

- All patients (N=3316) recruited into DART. 2957 were eligible for this analysis.
- Baseline clinical characteristics recorded + questionnaire for socio-demographic characteristics.

Data collection at regular clinic visits.

- Four weekly visits to refill ART drugs (to next scheduled visit).
- All unused drugs documented (separate documentation for each drug)
- Side effects and other changes in drug regimes noted.
- Simple questions on adherence were asked.



Adherence definitions



1) Objective measures

- The objective measure used was drug possession ratio (DPR), defined as percentage of time that patients could have taken the correct ART drugs.

2) Self reported measures

- Secondary measures of adherence were taken from the structured adherence questionnaire.
 - "Missed a treatment dose in last 4 days"
 - "Missed dose in last month"
 - "Were late for scheduled visit"
 - "Forgot to take pills at weekend"



Data & Statistical methods



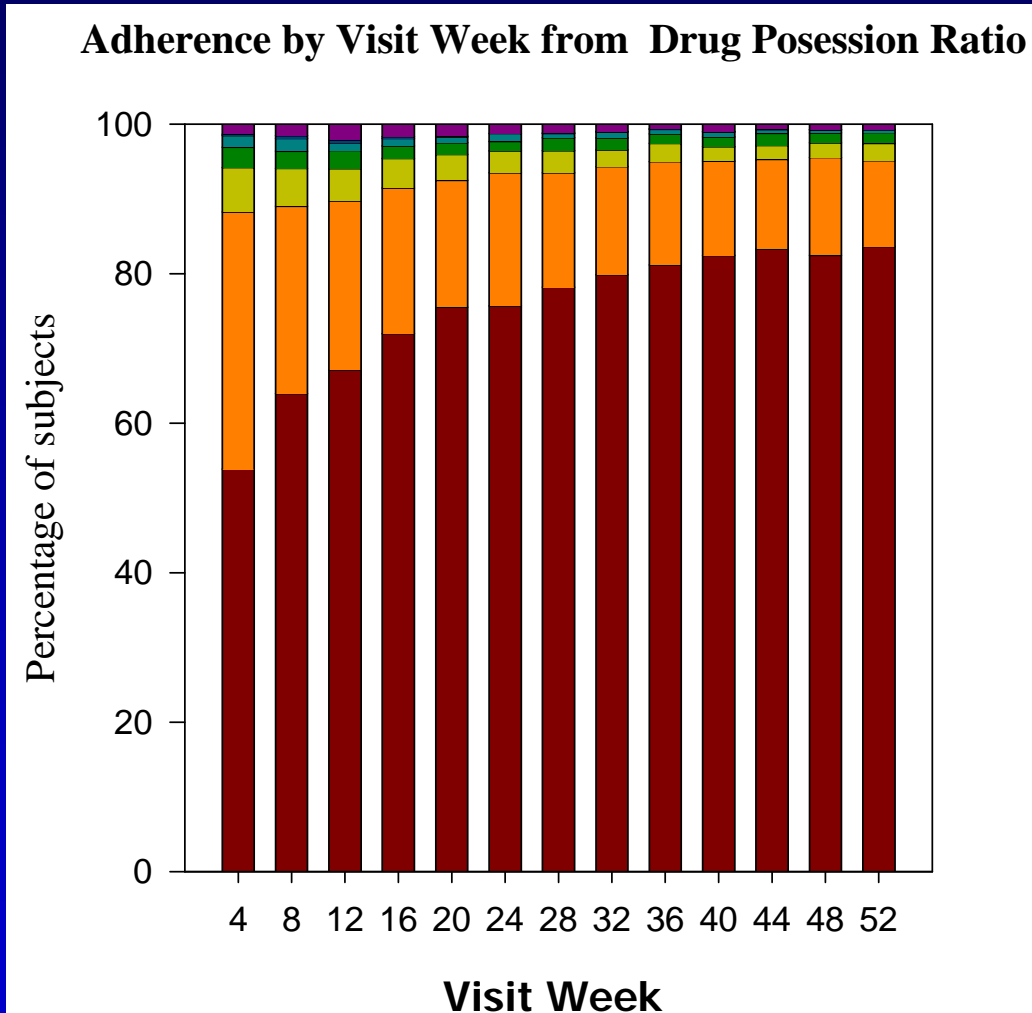
- At each clinic visit DPR adherence categorised. Analysis of 100% DPR or $\geq 95\%$ DPR as binary adherence measure

- Individual clinic visits used:
 - ❑ To assess baseline characteristics associated with 100% DPR adherence (using GEE).
 - ❑ To compare questionnaire responses to 100% DPR

- Summary of adherence over year & over each quarter:
 - ❑ To analyse change in viral load from baseline (using GEE).
 - ❑ Viral load suppression at end of quarter (12, 24, 36 & 48 weeks)



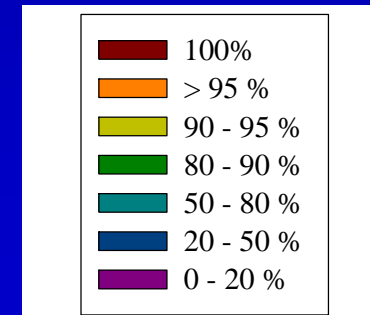
Adherence in the first year



Initial adherence
(week 4) <60%

Rapid improvement
in adherence over 12
weeks

Continued
improvement over 52
weeks





Results



Clinic visit data show adherence increases over first year.
Perhaps related to initial side effects, improvement in health, or better understanding of tablet taking.

Summary measures of adherence by patients over time:

➤ **95% DPR** was achieved by:

2154 (73%) at every visit in the first 12 weeks

2260 (76%) for at least 12 out of 13 visits in the year

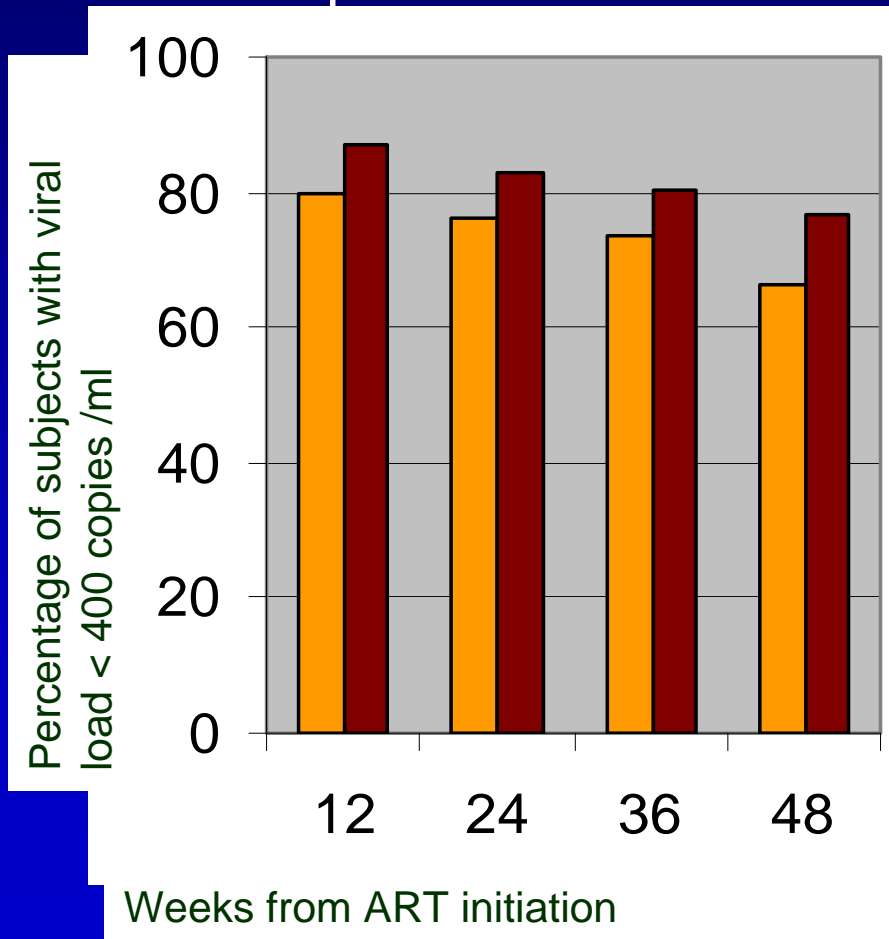
Only 161 (7%) were poor adherers because they failed to achieve >95% DPR adherence for 3 or more of the clinic visits in the year.



HIV-1 RNA suppression by adherence in a subset of 278 participants



Adherence assessed by DPR in 12 weeks prior to viral load




Viral load suppression was greater in those with 100% adherence, and widened over time, but even at 48 weeks still not significant ($p=0.33$)

- < 100% adherence in last 12 weeks
- 100% adherence in last 12 weeks



Change in log₁₀HIV-1 RNA from baseline and association with different adherence measures



Factor	Univariable model ^a			Multivariable* model ^b		
	Log	(95% CI)	p	Log	(95% CI)	p
100% DPR	-0.31	(-0.58, -0.03)	0.031	-0.32	(-0.60,-0.05)	0.020
Not Reported late for scheduled visit	-0.10	(-0.67, 0.48)	0.741	-0.17	(-0.80, 0.45)	0.583
Not Missed treatment dose in last 4 days	-0.20	(-0.57, 0.18)	0.311	-0.27	(-0.65, 0.10)	0.156
Not Missed any ART within last month	-0.23	(-0.53, 0.07)	0.126	-0.30	(-0.59, -0.003)	0.048
Not reported forgetting pills at the weekend	-0.51	(-1.02, 0.01)	0.054	-0.58	(-1.09, -0.07)	0.025

^a adjusting for baseline viral load, ^b adjusting for baseline viral load, baseline CD4 counts and time on ART

Adherence was assessed over the 12 weeks prior to the viral load measurement.

Interval regression used as data are left censored for undetectable viral loads

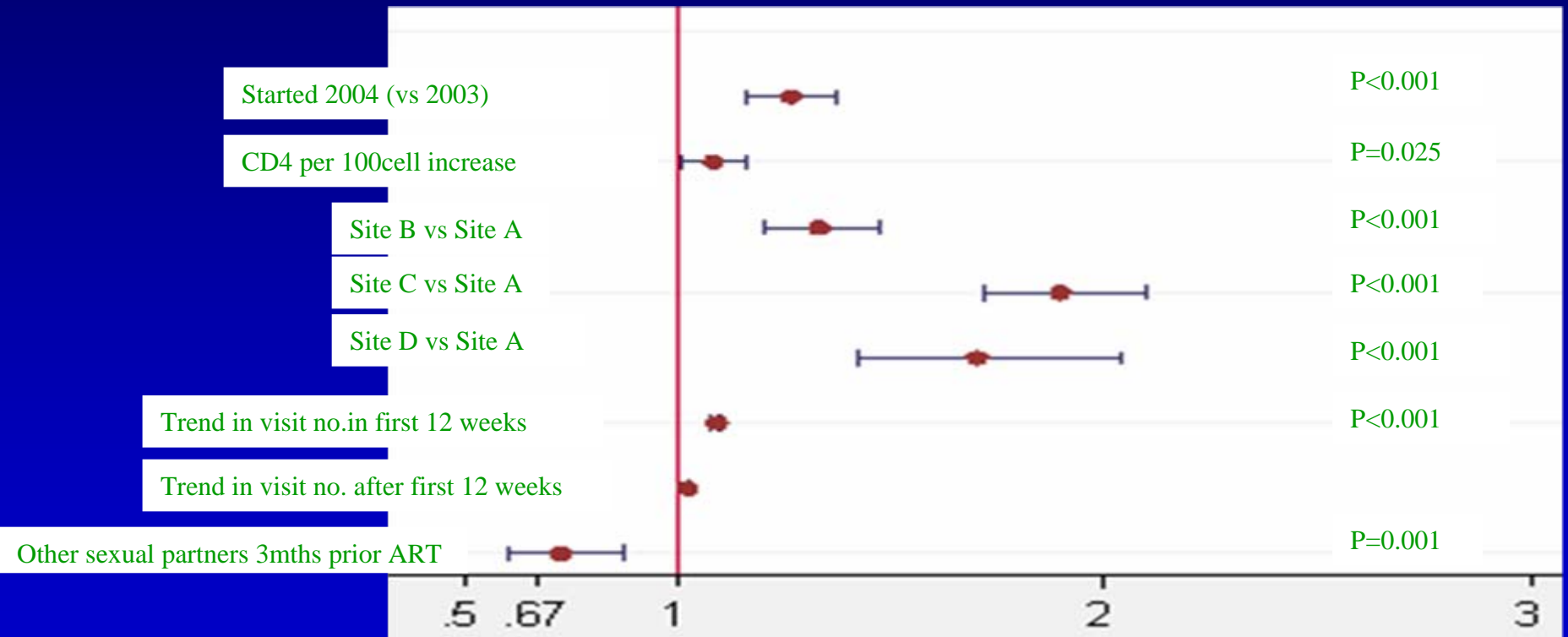


Baseline predictors of good adherence



Good adherence defined as 100% DPR

Analysis over all clinic visits in the first 52 weeks from ART initiation.



Clinic characteristics are important. It is also important to identify patients that are more likely to struggle with adherence.



Responses to adherence questions and their association with DPR



- All four structured adherence simple questions were associated with adherence measured by 100% mean DPR. In a multi-variable analysis, an independent significant association was seen only for missed dose in last month (OR=17).
- The simple questions are good at identifying good adherers but not good at identifying poor adherers. Sensitivity in identifying poor adherers for 100% DPR of the question “not missed ART within last month” was 40%.



Discussion I



Adherence increases over the first year.

- In other studies adherence decreased over time.
- Perhaps indicate improvements in patients health, and understanding over time or patients learning that it's good to come back with an empty bottle.

What should we measure?

- Drug possession ratio is significantly associated with viral load suppression. DPR shown to be useful in other studies.
- Responses to simple questions are also predictive of viral load changes, and may be useful proxy for DPR, and are easier to collect.

Baseline predictors of good adherence

- More attention to those with Lower CD4, and reporting sexual partners 3 months prior to ART initiation by extra counseling
- Differences in sites - opportunity for sites to learn from other sites



Discussion II



- In this large cohort of previously untreated African individuals initiating ART in rural and urban centres.
 - ❑ Excellent clinic attendance over the first year on ART
 - ❑ Follow up included 93% of those enrolled

Adherence measured by pill counts and drug possession ratio were high at each visit

- ❑ Over the course of the year adherence increased
- ❑ Only 12% of patients maintained consistently high adherence over the whole year.
- ❑ Most patients had high adherence most of the time, with only one or two visits with <95% adherence
- ❑ <1% participants never achieved high adherence during the first year.



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