Does HAART Efficacy Translate to Effectiveness? Evidence for a Trial Effect

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Abstract

Background: Patients who participate in clinical trials may experience better clinical outcomes than patients who initiate similar therapy within routine clinical care (trial effect), but no published studies have evaluated a trial effect in HIV clinical trials.

Methods: To examine a trial effect we compared virologic suppression (VS) among patients who initiated HAART in a clinical trial versus in routine clinical care. VS was defined as a plasma HIV RNA ≤400 copies/ml at six months after HAART initiation and was assessed within strata of early (1996–99) or current (2000–06) HAART periods. Risk ratios (RR) were estimated using binomial models.

Results: Of 738 persons initiating HAART, 30.6% were women, 61.7% were black, 30% initiated therapy in a clinical trial and 67% (n = 496) had an evaluable six month HIV RNA result. HAART regimens differed between the early and current periods (p < 0.001); unboosted PI regimens (55.6%) were more common in the early and NNRTI regimens (46.4%) were more common in the current period. Overall, 78% (95%CI 74, 82%) of patients achieved VS and trial participants were 16% more likely to achieve VS (unadjusted RR 1.16, 95%CI 1.06, 1.27). Comparing trial to non-trial participants, VS differed by study period. In the early period, trial participants initiating HAART were significantly more likely to achieve VS than non-trial participants (adjusted RR 1.33; 95%CI 1.15, 1.54), but not in the current period (adjusted RR 0.98; 95%CI 0.87, 1.11).

Conclusions: A clear clinical trial effect on suppression of HIV replication was observed in the early HAART period but not in the current period.

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Introduction

A trial effect occurs when study participants experience a benefit merely by the act of trial participation. The effect may arise due to a treatment effect (newer, better or experimental treatments available to trial participants but unavailable outside the trial), a protocol effect (differences in the way treatment regimens are delivered), a care effect (differences in care), a Hawthorne effect (behavior change secondary to being under observation) or a placebo effect (“psychologically mediated” benefits that arise due to being in a trial) [1–4]. A trial effect should be distinguished from apparent effects (biases) particularly selection bias (differences between trial and non-trial participants).

The evidence for or against a trial participation benefit or trial effect is inconclusive [1,3,5–7]. Current evidence, derived primarily from cancer trials, is limited in breadth, quality and quantity. HIV-related clinical trials provide an excellent substrate for the measurement of a trial effect. HIV infection is a chronic illness with well-characterized treatments and HIV-related outcomes are easily measured and clinically meaningful.

To determine whether a trial effect exists in HIV clinical trials, we compared virologic suppression (VS) between HIV-infected patients who were antiretroviral naive and who initiated highly active antiretroviral therapy (HAART) either in a trial or as part of routine medical care. The benefit of HAART to patients is unquestionable. However, if participation in clinical trials leads to a beneficial trial effect, careful consideration of the mechanisms and consequences of that trial effect would be needed. At the least, aspects of the trial effect, such as protocol effect or care effect, may need to be incorporated into clinical care to achieve similar results. Furthermore, the existence of a positive trial effect might suggest reduced generalizability of clinical trials data to non-trial participants. Finally, clinical trials data provide evidence for the care and treatment guidelines of HIV infected persons and a trial
effect might oblige guidelines to caution about possible differences in outcome in non-trial settings.

Methods

Study design
We conducted a secondary data analysis using the University of North Carolina (UNC) Center for AIDS Research (CFAR) HIV/AIDS clinical cohort (UCHCC). This cohort, comprising adult (≥18 years) HIV-infected persons who receive health care at the UNC Hospital Infectious Diseases (ID) clinic, has been described previously [8,9]. Over 95% of the UNC ID clinic population has consented to participate in the UCHCC and non-consenting patients do not differ significantly from those who provide consent. All patients provided written informed consent, and the study was approved by the Biomedical Institutional Review Board of the University of North Carolina at Chapel Hill.

Study population
Antiretroviral naïve HIV-infected adults who initiated HAART from April 1996 to December 2006 were included in this analysis. HAART was defined as any combination of three or more antiretroviral agents, or a combination of at least one protease inhibitor (PI) plus one non nucleoside reverse transcriptase inhibitor (NNRTI) with or without additional agents. Patients were characterized as trial participants if HAART was initiated as part of a clinical trial. Patients co-infected with HCV and/or HBV were included in the analysis. Clinical trials included NIH AIDS Clinical Trial Group (ACTG) supported or industry sponsored trials.

Variable Specification
We defined the outcome of virologic suppression (VS) as having a plasma HIV RNA level ≤400 copies/mL at six months from the date of HAART initiation, using a window of five to nine months and selecting the plasma HIV RNA value nearest six months if more than one value occurred in this window. We considered trial participation as the factor of interest. A joint categorization of gender (male/female) and sexual orientation (heterosexual/homosexual/bisexual) resulted in a variable with three categories 1) men who have sex with men (MSM) 2) heterosexual men and 3) women. Bisexual men were placed in the MSM category. Additional variables included insurance status (Medicaid/Medicare, none and private/other), distance traveled from home to the UNC Infectious Diseases (ID) clinic in miles, and the duration in month’s from the date of HIV diagnosis to HAART initiation.

Selected clinical laboratory values that may influence trial participation, initiation of HAART and treatment outcome including baseline CD4 cell count, plasma HIV RNA level, hemoglobin, creatinine, alanine aminotransferase [ALT], and absolute neutrophil count [ANC] were assessed. For laboratory results not available at baseline an extended window spanning 180 days before and up to 14 days after the date HAART was initiated was considered. ALT, ANC, creatinine and hemoglobin were categorized as normal or abnormal using gender appropriate normal ranges.

Treatment characteristics included the type of HAART and the date HAART was initiated. HAART was categorized as 1) a ritonavir-boosted protease inhibitor (PI) or two PIs combined with either two or three nucleoside reverse transcriptase inhibitors (NRTIs) 2) a NNRTI combined with either two or three NRTIs 3) an unboosted PI combined with either two or three NRTIs 4) a NNRTI and a PI with or without NRTIs and 5) three NRTIs. The year HAART was initiated was dichotomized to represent the differences in initial treatment regimens as the early HAART period (1996-99) and the current HAART period (2000-06) [10].

Statistical Analyses
Baseline differences in demographic, clinical, treatment and laboratory characteristics were explored using the chi square test, t test and Wilcoxon rank sum test with 2-sided P values reported in all cases.

We estimated an unadjusted risk ratio (RR) and a 95% Confidence Interval (CI), to assess the relationship between trial participation and the risk of VS at six months after HAART initiation. Multivariable analyses were performed using Poisson regression with no offset and a robust variance estimator to provide an estimate of the risk ratio [11–13]. We assessed effect measure modification with interaction terms between relevant covariates. Effect measure modification was considered to be present if the coefficient estimate for the interaction term differed significantly from zero (p < 0.1). A significant interaction was noted between trial participation and the period in which HAART was initiated. Therefore all analyses were stratified by HAART period.

Confounding was evaluated by both substantive (a priori) and change in estimate criteria. We used a manual backward elimination procedure to arrive at the final model. A covariate was retained as a confounding variable if it changed the effect estimate by at least 10 percent. Two variables ‘type of HAART’ and ‘CD4 cell count’ did not change the effect estimate by ≥10% but were included in the final model based on substantive knowledge.

Sensitivity Analyses
Our primary analysis involved a complete case analysis. HIV RNA result at the six month time point was unavailable for 33% of patients. We completed sensitivity analyses to explore the potential impact of the missing data. We conducted an extreme case analysis to obtain the upper and lower bounds of the RR [14–16]. For this we assumed that among the patients with missing outcome, every trial participant achieved virologic success while non-trial participants were virologic failures and vice versa. A second analysis assigned virologic failure to all or a varying fraction of missing values for trial and non-trial participants [14–16].

Intercooled Stata (version 9.0), Stata Corporation, (College Station, TX) was used for all analyses.

Results
Sample Characteristics
Of the 738 ARV naïve persons initiating HAART, 67% (n = 496) had an HIV RNA result available at six months. Results for this group (complete cases) are presented here (Table 1). The mean age of patients was 38.5 years (standard deviation 9.9), 37.3% were women, 60.1% were black, 27.4% were white, 8.3% were Hispanic and 34% initiated therapy in the context of a clinical trial. Trial participants were more likely to be MSM (42.3%), non Black (41.4%) and not have insurance (42.9%) compared to non-trial participants (14.4%) fewer trial participants (83.3%) reported injection drug use. No significant between group differences were observed in baseline HIV RNA level or CD4 cell count. Trial participants were slightly more likely to have a viral load (VL) at or close to the 6 month time point. However, the distribution around the 6 month time point was similar in that similar proportions had VL before and after 6 months in the two treatment groups (trial and non-trial).
### Table 1. Baseline sample characteristics for study population, complete cases and comparing trial to non-trial participants restricted to complete cases.

| Study Population Complete Cases | Non-Trial Participants | Trial Participants | p value* |
|--------------------------------|------------------------|--------------------|----------|
| N = 738 %                     | N = 496 %              | N = 327 %          | N = 169 % |       |
| **Demographic and Behavioral Characteristics** |                        |                    |          |       |
| Age (years)                   |                        |                    |          |       |
| <40                           | 429 58.1               | 273 55             | 183 56   | 93 53.3 | 0.6 |
| Gender/sexual preference      |                        |                    |          |       |
| MSM\(^1\)/Bisexual men        | 252 34.2               | 175 35.3           | 101 30.9 | 74 43.8 | 0.02|
| Heterosexual men              | 260 35.2               | 165 33.2           | 114 34.9 | 51 30.2 |     |
| Heterosexual women            | 226 30.6               | 156 31.5           | 112 34.2 | 44 26.0 |     |
| Race                          |                        |                    |          |       |
| Black                         | 455 61.7               | 298 60.1           | 211 64.5 | 87 51.5 | 0.005|
| Non Black\(^2\)              | 283 38.3               | 198 39.9           | 116 35.5 | 82 48.5 |     |
| **Access to Care Characteristics** |                        |                    |          |       |
| Insurance Status              |                        |                    |          |       |
| Public\(^3\)                 | 191 26.3               | 126 25.9           | 103 31.8 | 23 14.1 | 0.001|
| None                          | 276 38.1               | 168 34.6           | 96 29.7  | 72 44.2 |     |
| Private/Other                 | 258 35.6               | 192 39.5           | 124 38.4 | 68 41.7 |     |
| Distance to ID\(^4\) clinic (miles) |                    |                    |          |       |
| <50                           | 182 24.7               | 130 26.3           | 77 23.6  | 53 31.4 | 0.06|
| >50                           | 527 71.3               | 365 73.7           | 249 76.4 | 116 68.6 |     |
| **Clinical Characteristics**  |                        |                    |          |       |
| CD4 cells/uL                  |                        |                    |          |       |
| ≤200                          | 321 56.6               | 257 57.6           | 151 54.1 | 106 63.4 | 0.1 |
| >200-350                      | 107 18.9               | 81 18.2            | 53 19.0  | 28 16.8 |     |
| >350                          | 139 24.5               | 108 24.2           | 75 26.9  | 33 19.8 |     |
| Mean HIV RNA (log\(_{10}\)) (sd) | 4.7 (1.0)            | 4.9 (1.0)          | 4.7 (1.0) | 4.8 (1.0) | 0.6 |
| Diagnosis to treatment (months) |                        |                    |          |       |
| ≤3                            | 250 38.9               | 168 37.4           | 116 37.2 | 52 38.0 | 0.9 |
| >3                            | 393 61.1               | 281 62.6           | 196 62.8 | 85 62.0 |     |
| **Treatment Characteristics** |                        |                    |          |       |
| HAART Initiation Year         |                        |                    |          |       |
| 1996-99                       | 266 36.0               | 161 32.5           | 124 37.9 | 37 21.9 | 0.001|
| 2000-06                       | 472 64.0               | 335 67.5           | 203 62.1 | 132 78.1 |     |
| HAART category\(^5\)         |                        |                    |          |       |
| 2 or 3 NRTI plus PI/r or 2 PI | 128 17.4               | 99 20.0            | 39 11.9  | 60 35.5 | 0.001|
| 2 or 3 NRTI plus NNRTI       | 288 39.0               | 192 38.7           | 132 40.4 | 60 35.5 |     |
| 2 or 3 NRTI plus PI (unboosted) | 218 29.5               | 134 27.0           | 116 35.4 | 18 10.7 |     |
| NNRTI/PI +/- 2 NRTI          | 55 7.5                 | 40 8.1             | 20 6.1   | 20 11.8 |     |
| 3 NRTI                       | 49 6.6                 | 31 6.3             | 20 6.1   | 11 6.5 |     |
| **Other Laboratory Parameters** |                        |                    |          |       |
| ANC\(^6\) (10^\(_9\))/L       |                        |                    |          |       |
| Normal                       | 348 47.2               | 268 62.2           | 173 65.3 | 95 57.2 | 0.09|
| Abnormal                     | 221 30.0               | 163 37.8           | 92 34.7  | 71 42.8 |     |
| Hemoglobin (g/dL)            |                        |                    |          |       |
| Normal                       | 258 34.9               | 195 41.1           | 116 43.6 | 79 47.6 | 0.4 |
| Abnormal                     | 311 42.1               | 237 54.9           | 150 56.4 | 87 52.4 |     |
| Creatinine (mg/dL)           |                        |                    |          |       |
| Normal                       | 685 93.1               | 462 93.2           | 298 91.1 | 164 97 | 0.01|
| Abnormal                     | 51 6.9                 | 34 6.8             | 29 8.9   | 5 3.0 |     |
Clinical Trials
Patients participated in 13 different clinical trials, nine sponsored by the AIDS Clinical Trials Group (ACTG) and four by pharmaceutical companies (Table 2) [17–30]. All but two of the trials were Phase III or IV. Two ACTG trials and one industry sponsored trial enrolled patients in the early period, and seven ACTG and three industry sponsored trials enrolled patients in the current HAART period.

HAART Regimens
The composition of HAART regimens significantly differed between trial and non-trial participants (p = 0.001). Trial participants were more likely to be initiated on a boosted PI regimen (60.6%) while non-trial participants were more likely to be initiated on an NNRTI based regimen (68.8%) (p = 0.001). Most patients initiating an NNRTI regimen received efavirenz (85%) while the majority of those initiating a boosted PI regimen received lopinavir/ritonavir (70.8%). Of the 134 patients who received unboosted PI regimens, 64% were initiated on nelfinavir. The most commonly used nucleoside/nucleotide backbone was lamivudine/zidovudine (49.7%), followed by lamivudine/ stavudine (14.7%), tenofovir/emtricitabine or lamivudine (13.8%), and lamivudine/abacavir (7%).

In both the early and current periods, HAART regimens differed between trial and non-trial participants with more trial participants initiating boosted PI regimens and more non-trial participants initiating NNRTI based regimens (P<0.05) (Figure 1).

Effect of trial participation on virologic suppression
Overall, 78% of patients achieved VS (95% CI 74, 82). Trial participants were 16% more likely to achieve VS when compared to non-trial participants (RR 1.16, 95% CI 1.06, 1.27). However the magnitude of this difference was dependent on the period in which HAART was initiated (early versus current). We thus present our results stratified by HAART period.

The effect of trial participation on VS differed by the period in which HAART was initiated (p = 0.001). In the early period, more trial participants achieved VS than non-trial participants (RR 1.42; 95% CI 1.24, 1.54). Although a difference was also observed in the current period, it was smaller and not statistically significant (RR 1.07; 95% CI 0.95, 1.19) (Table 3). After adjustment for age, distance traveled to receive care at UNC ID clinic, baseline HIV RNA levels, CD4 cell count, months from HIV diagnosis to HAART initiation, creatinine and type of HAART, trial participants remained more likely to achieve virologic suppression than non-trial participants (RR 1.33; 95% CI 1.15, 1.54) in the early period. By contrast, in the current period, virologic suppression of trial and non-trial participants was similar (RR 0.98; 95% CI 0.87, 1.11).

Missing Data and Sensitivity Analyses
The outcome of VS measured by an HIV RNA result within the specified 5-9 month window was unavailable for 242 (33%) patients. More non-trial participants (36.4%) had missing data than trial participants (24.6%) (p<0.05). Patients with missing HIV RNA results were similar to those with values in terms of age (mean age 37 vs. 39 years), race (65% vs. 60% black) and gender (29% vs. 31% female). Likewise, we found no differences in clinical characteristics (baseline HIV RNA and CD4 cell count) and laboratory parameters (ALT, ANC, hemoglobin) (all p values >0.05). However, more patients missing HIV RNA results were uninsured (45.2% vs. 34.6%) and fewer had private insurance (27.6% vs. 39.5%) (p = 0.004).

The proportion of patients experiencing virologic success or failure in each group or time period is not known and any assumption, including the primary analysis, has some bias. Therefore we performed a series of sensitivity analyses, in which the proportion of virologic successes and failures in patients with missing data were varied, including a missing equals failure (M = F) analysis (Figure 2). In the early period, all but one of the sensitivity analyses performed provided statistically significant risk ratios favoring trial participation. In the current period, of nine different sensitivity analyses (including the M=F analysis), trial participation was only favored in one extreme case analysis in which all trial participants with missing outcomes were considered virologic successes while non-trial participants were virologic failures (aRR 1.36, 95% CI 1.18, 1.55) (Figure 2).

Discussion
This study is the first to examine a trial effect in HIV clinical trials by comparing virologic suppression (VS) among antiretroviral (ARV) naive trial and non-trial participants initiating HAART. Close to two-thirds of treatment naive patients achieved virologic suppression six months after initiating HAART. The effect of trial participation varied by the period of HAART initiation. In the early HAART period (1996-99), trial participants achieved VS more commonly than non-trial participants.
However, in the current HAART period (2000-06), we found no difference in VS comparing trial to non-trial participants. Our observations were supported by the sensitivity analyses.

There may be several reasons why a trial effect was readily apparent in the early HAART period. Results from cancer trials have suggested a trial effect in trials conducted before 1986, a time of rapid change for cancer care and treatments[3]. This might also be the case in our study where during the early period, there were differences in the type of HAART with more trial participants initiated on an NNRTI/PI or boosted PI combination and fewer initiated on an unboosted PI regimen (i.e., a treatment effect). Even after controlling for differences in the type of HAART, the beneficial effect of trial participation in the early period persisted. Treatment regimens during this period were complex and associated with fairly significant side effects. Therefore, it is possible that trial participants benefited from both a care effect and a protocol effect resulting in better treatment outcomes. Furthermore, in the early period, HIV infection was associated with considerable morbidity and mortality which likely influenced patient’s attitudes towards HAART.

We believe our results demonstrate a true trial effect as we were able to address the challenge of identifying an optimal comparison group. Such a comparator group might comprise trial eligible subjects who declined trial participation but were similar in other baseline characteristics [3,5]. Although we are unable to state that non-trial participants were either trial eligible or were trial eligible refusers our data suggests that our two groups were comparable. First, both trial and non-trial participants were drawn from a single clinic population suggesting similarity between groups. Second, we increased between group homogeneity by restricting our study population to include only ARV naïve subjects. Third,
Antiretroviral Treatment by Trial Participation

Early Period (1996-1999)

No Trial

- Boosted PI: 3%
- NNRTI: 27%
- Unboosted PI: 58%

Trial

- Boosted PI: 16%
- NNRTI: 22%
- Unboosted PI: 35%

p < 0.05 comparing trial to non-trial participants

Current Period (2000-2006)

No Trial

- Boosted PI: 8%
- NNRTI: 22%
- Unboosted PI: 48%

Trial

- Boosted PI: 39%
- NNRTI: 41%
- Unboosted PI: 8%

p < 0.05 comparing trial to non-trial participants

Figure 1. Antiretroviral treatment by trial participation.

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We found no strong evidence supporting a trial effect in the current HAART period. Compared to the early HAART period, the proportion of non-trial participants who achieved VS increased, but we also noted a decrease in the proportion of trial participants who achieved this milestone. The enhanced treatment response in non-trial participants may be due to noteworthy improvements in ARV therapy between the early and current period. We controlled for treatment differences by restricting our definition of HAART and by categorizing the periods in which HAART was initiated. Finally, we examined detailed baseline demographic and clinical characteristics, as well as laboratory parameters and found no substantial differences between these two groups. Consequently, it is highly likely that most of our non-trial participants were trial eligible and that some proportion of them were trial eligible refusers.
HAART periods. Other cohorts examining the efficacy of triple combination therapy have reported chronological improvements in VS [10,31]. Like other studies, we observed changes in the initial HAART regimen with a significant increase in the use of a boosted PI or NNRTI and a decline in the use of an unboosted PI [10]. The superiority of a NNRTI or boosted PI versus unboosted PI regimens in ARV naïve persons has been clearly demonstrated [19,32–33]. Other improvements to ARV therapy include ease of use (dosing frequency and pill burden), better tolerability and lower toxicity. Moreover, calendar time may also be associated with other unmeasured factors such as provider experience, medication adherence and increased patient awareness about the benefits of and improvements to HAART. The period in which HAART was initiated likely acted as a surrogate for these temporal factors.

The improvements to ARV therapy in the current period may have lessened the impact of the care effect for trial participants. Additionally, in the current period HIV infection began to be regarded as a chronic but treatable infection which may have influenced patient attitudes. Thus the potential interaction between care effect and patient attitudes was likely diminished resulting in a more modest response to treatment among trial participants. Moreover, in the current period the motivation for participation in clinical trials may have changed with more patients choosing clinical trials for objective (e.g. financial) and subjective (e.g. trust in providers) reasons that we were unable to measure and which may have decreased the likelihood of success.

Our definition of VS (plasma HIV RNA ≤400 copies/ml at six months) may have limited our ability to detect a trial effect in the current period. A care effect may have needed a longer duration to become apparent in the current period as, over time, the risk for non-adherence increases and the structure of a clinical trial may improve adherence to ARV therapy and to care. Possibly, a longer outcome period might have favored trial participants and supported a trial effect. In the current period, all but one of the trials included in our study was a Phase III or later trial therefore we feel that these results are most applicable to Phase III or later trials.

Since this study was conducted at a single center these results may not be demonstrable in other settings. In our center as clinicians and clinical trial investigators overlap or are in very close contact clinical practice may be influenced by the ongoing trials. One third of our cohort was missing the outcome of VS at the six month time point. Reassuringly, patients with missing data were similar to those for whom complete data was available. Results of sensitivity analyses conducted to determine the potential influence

### Table 3. Risk Ratios for virologic suppression by trial participation within strata of HAART period.

|                      | Risk Ratios (95% Confidence Intervals) | Unadjusted | Adjusted** |
|----------------------|---------------------------------------|------------|------------|
| **Early HAART period (1996-99)** |                                       |            |            |
| Non-Trial Participants | 1                                     | 1          |            |
| Trial Participants    | 1.42 (1.24, 1.62)                      | 1.33 (1.15, 1.54) |
| **Current HAART period (2000-06)** |                                       |            |            |
| Non-Trial Participants | 1                                     | 1          |            |
| Trial Participants    | 1.07 (0.95, 1.19)                      | 0.98 (0.87, 1.11) |

**adjusted for age, distance traveled to receive care at UNC ID clinic, baseline HIV RNA levels, CD4 cell count, months from HIV diagnosis to HAART initiation, creatinine, type of HAART.

*Figure 2. Sensitivity Analysis: Risk Ratios for viral suppression following different adjustment schema for missing data.*

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of the missing data substantiate the results of the primary analysis and suggest that the observed effects, or lack thereof, are unlikely to be attributable to missing data. Potential sources of bias, including unmeasured confounders, could either mask or inflate a trial effect [34,35]. We defined VS based on a single measurement, to minimize bias due to possible differences in measurement frequency between trial and non-trial participants. In our study, care setting bias and clinician selection bias appear less likely since all patients were followed at the UNC Infectious Disease Clinic and received their health care from a single group of clinicians [1,3].

We believe this is the first study to clearly and rigorously demonstrate a trial effect in HIV clinical trials. This observation is extremely important for later lines of ARV therapy (e.g., salvage therapy) which are more complex and where the trial effect that we observed in the early HAART period might still occur due to the interplay between patient attitudes, protocol effect and care effect. Also important is the lack of strong support for a trial effect in the current period. This has significant public health implications as it demonstrates that HAART achieves comparable VS both in clinical trials and routine clinical care. These results suggest that in the current period the efficacy of HAART is no different from the effectiveness indicating that the results of clinical trials for treatment naïve HIV infected patients are generalizable to the larger population. Clinicians and public health officials can have confidence that treatment guidelines that are formulated based on clinical trials data are relevant to routine clinical care and can be extrapolated to clinical care.

Although, we found no strong evidence for a trial effect in the current period, there are advantages to participation in clinical trials including access to newer treatments, and clinical monitoring by a dedicated team of study personnel. In keeping with other studies, we did not observe worse outcomes for trial participants in either period [36–40]. Therefore, we feel, a reasonable corollary is that participation in HIV treatment trials does not increase the risk of an adverse outcome. Most studies do not refute that there is a positive benefit to trial participation, though the magnitude of the benefit may differ and may depend on the type of trial [1,41,42]. Lastly, there is an inherent altruism involved in trial participation which may afford patients a sense of pride and self worth [43–46].

In summary, we demonstrated, for the first time, that participation in HIV clinical trials resulted in an improved outcome compared to clinic-based treatment (i.e. trial effect), in ARV treatment naïve patients drawn from the same population, even after controlling for multiple potential confounders. This trial effect, however, was only observed in the early HAART period and we found no strong evidence for a trial effect in HIV clinical trials in treatment naïve patients in the current HAART period. This lack of a trial effect in the current HAART period argues that for studies of combination ARV therapy in treatment naïve individuals the efficacy demonstrated in clinical trials is likely to predict the effectiveness of the therapy in broader treatment populations.

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Author Contributions

Conceived and designed the experiments: PM DW JE. Performed the experiments: PM WM JE. Analyzed the data: PM. Contributed reagents/materials/analysis tools: PM WM JE DW AA PL. Wrote the paper: PM WM JE DW AA PL.

References

1. Brauholz DA, Edwards SJ, Lifdor JF (2001) Are randomized clinical trials good for us (in the short term)? Evidence for a “trial effect”. J Clin Epidemiol 54: 217–224.
2. Lantos JD (1999) The “inclusion benefit” in clinical trials. J Pediatr 134: 130–131.
3. Peppercorn JM, Weeks JC, Cook EF, Joffe S (2004) Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. Lancet 363: 263–270.
4. Silverman WA (2002) Disclosing the “inclusion benefit”. J Perinatol 22: 261–262.
5. ECRI Evidence Report: Patients’ reasons for participating in clinical trials and effect of trial participation on patient outcomes. (2002) Available at: https://www.ecri.org/Document/42\Clinical_Trials_Patient_Guide/031\Evidence_Report.pdf. Accessed June 27, 2008.
6. Stiller CA (1994) Centralised treatment, entry to trials and survival. Br J Cancer 70: 352–362.
7. Vist GE, Hagen KB, Devereaux PJ, Bryant D, Kristoffersen DT, Oxman AD (2003) Systematic review to determine whether participation in a trial influences outcome. BMJ 330: 1175.
8. Napaevnik S, Edwards D, Stewart P, Stalzer B, Matteson E, et al. (2005) HIV-1 drug resistance evolution among patients on potent combination antiretroviral therapy with detectable viremia. J Acquir Immune Defic Syndr 40: 34–40.
9. Napaevnik S, Eron JJ Jr., McKaig RG, Heine AD, Menezes P, Quinlan E (2006) Factors associated with fewer visits for HIV primary care at a tertiary care center in the Southeastern U.S. AIDS Care 18(Suppl 1): S45–S50.
10. Lampé FC, Gaylen JM, Staszewski S, Johnson MA, Pradier C, et al. (2006) Changes over time in risk of initial virological failure of combination antiretroviral therapy: a multicohort analysis, 1996 to 2002. Arch Intern Med 166: 521–528.
11. Barros AJ, Hirakata VA (2003) Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. BMC Med Res Methodol 3: 21.
12. McNutt LA, Wu C, Xue X, Hafner JP (2003) Estimating the relative risk in cohort studies and clinical trials of common outcomes. Am J Epidemiol 157: 940–943.
13. Zou G (2004) A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol 159: 702–706.
14. The European Agency for the Evaluation of Medicinal Products (2001) Evaluation of Medicines for Human Use. Committee for Proprietary Medicinal Products. Points to Consider on Missing Data. London, 15 November 2001.
15. Delucchi KL (1994) Methods for the analysis of binary outcome results in the presence of missing data. J Consult Clin Psychol 62: 569–575.
16. Hollis S (2002) A graphical sensitivity analysis for clinical trials with non-ignorable missing binary outcome. Stat Med 21: 3823–3834.
17. Kalayjian RC, Landay A, Pollard RB, Taub DD, Gross BH, et al. (2003) Age-related immune dysfunction in health and in human immunodeficiency virus (HIV) disease: association of age and HIV infection with naive CD8+ cell depletion, reduced expression of CD28 on CD8+ cells, and reduced thymic volumes. J Infect Dis 187: 1924–1933.
18. Riddler SA, Hauber R, DiRienzo AG, Perples L, Powderly WG, et al. (2008) Class-Sparing regimens for initial treatment of HIV-1 infection. N Engl J Med 350: 2095–2106.
19. Robbins GK, De Gruttola V, Shafer RW, Smeaton LM, Snyder SW, et al. (2003) Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. N Engl J Med 349: 2304–2315.
20. Shafer RW, Smeaton LM, Robbins GK, De Gruttola V, Snyder SW, et al. (2003) Comparison of four-drug regimens and pairs of sequential three-drug regimens as initial therapy for HIV-1 infection. N Engl J Med 349: 2304–2315.
21. Zolopa A AJ, Komarow L, Sanchez A, et al. (2006) Immediate vs Deferred ART in the Setting of Acute AIDS-related Opportunistic Infection: Final Results of a Randomized Strategy Trial, ACTG A5164. [Abstract 142]. 15th Conference on Retroviruses and Opportunistic Infections, Boston 2008.
22. Eron J, Jr., Yeni P, Gallo R, Jr., Estrada V, Dejesus E, et al. (2006) The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. Lancet 368: 476–482.
23. Fischl MA, Ribaudo HJ, Collier AC, Erice A, Giuliano M, et al. (2003) A randomized trial of 2 different 4-drug antiretroviral regimens versus a 3-drug regimen, in advanced human immunodeficiency virus disease. J Infect Dis 188: 625–634.
