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Access to Medications and Medical Care After Participation in HIV Clinical Trials: A Systematic Review of Trial Protocols and Informed Consent Documents

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Abstract

Background—Expectations regarding receipt of medications and medical care after clinical trials conclude may inform decisions about trial participation. We describe the frequency with which these posttrial services are described in the protocols and informed consent forms (ICFs) of antiretroviral drug (ARV) trials.

Method—We systematically reviewed protocols and ICFs from Phase 3 and 4 antiretroviral trials in adults (≥12 years) from 1987 to 2006. Pharmaceutical industry-sponsored trials were selected from US Food and Drug Administration (FDA) documentation and Clinicaltrials.gov. Trials administered by the AIDS Clinical Trials Group (ACTG) were selected from the ACTG online registry. ACTG- and industry-provided protocols and ICFs were reviewed in full. The primary outcome was any mention of posttrial services, defined as any text regarding posttrial medications or medical care.

Results—Complete trial documents were available for 31 (48%) of 65 trials meeting inclusion criteria. Documents from 14 trials (45%) mentioned any posttrial service: 12 (39%) mentioned medications, and 5 (16%) mentioned medical care. Payment for trial participation (74%) and for care for trial-related injury (94%) were mentioned more often than were posttrial services.

Conclusions—Posttrial medications or medical care was mentioned in the trial documents of <50% of reviewed antiretroviral trials. Improved efforts are needed to clearly describe posttrial services in clinical trial protocols and ICFs. and ICFs.

Keywords

clinical trials; HIV; posttrial services; trial protocols

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In countries without comprehensive national health care systems and in resource-limited settings, clinical trial participants may lack access to medications and medical care after trials conclude. [1] Since approximately 2000, investigators, research participants, and ethicists have engaged in a vigorous debate regarding whether participants in clinical trials are entitled to receive posttrial medications and medical care and whether these services should be provided by trial sponsors, local agencies, or national governments. The ethical debate has included divergent opinions regarding three primary issues: (1) whether receipt of posttrial services constitutes a fair benefit or an undue inducement to research participants,[1–4] (2) whether providing posttrial services unfairly prioritizes research participants over other community members,[5–7] and (3) whether an obligation to provide such services creates an excessive burden for trial sponsors, thus reducing their incentive to conduct research.[5,6] In addition, particularly for trials conducted in resource-limited settings, it has been suggested that local governments and non-governmental organizations may be better suited than trial sponsors to provide posttrial services.[7–9]

Limited survey data suggest that patients may have strong desires and expectations to receive posttrial services. Ninety-eight percent of participants in an international HIV trial stated that an efficacious study drug should be provided after trial conclusion to, at minimum, trial participants; 81% of these participants stated that the medication should be provided to all HIV-infected patients in the world.[1] In a second study, patients also felt that trial participants should receive lifelong medical care for both trial-related and -unrelated conditions.[10] There is little published literature on expectations regarding posttrial services, or receipt of such services, for patients with conditions other than HIV infection.

Accurate expectations regarding posttrial services by research participants, investigators, and human subjects committee members may be particularly important for trials of antiretroviral drugs (ARVs) for HIV infection, given recent evidence of clinical risks following treatment interruption.[11–13] However, providing long-term ARVs requires infrastructure, personnel, and clinical and laboratory monitoring that add substantial costs to the expense of ARVs alone and may not be available after trials conclude in resource-poor locations.[6]

Despite the importance of posttrial services, international research guidelines offer few specific recommendations regarding these services.[14–21] The Declaration of Helsinki asserts that posttrial access to interventions studied in trials should be “assured” to trial participants and that plans for posttrial services should be explicitly described in trial protocols. [14] However, other widely cited research guidelines, including those of the US National Institutes of Health (NIH) Division of AIDS,[15] state only that posttrial access to medications and medical care should be “considered” in the trial planning process.[16–21]

Protocols and informed consent forms (ICFs) comprise important sources of information regarding trial procedures and trial-related benefits to participants, investigators, and human subjects committee members. Our objective was to characterize the ways in which posttrial services are described in protocols and ICFs of ARV clinical trials. We conducted a systematic review of trial protocols and template ICFs, and we report on the frequency with which these documents explicitly mention and/or offer to provide posttrial medications and medical care to trial participants.

METHOD

Clinical Trials Included

We identified all eligible Phase 3 and Phase 4 ARV trials in adults, sponsored by either the pharmaceutical industry or the NIH. Phase 3 trials were included to capture investigational medications with a high probability of demonstrating efficacy but not yet commercially

available, thereby creating a situation in which they would be desired by participants after trial completion. Phase 4 trials were included to evaluate situations in which patients might be expected to have another means of obtaining the study medication after trial completion, for example by prescription through their usual means of obtaining medical care.[22]

We used different methods to identify three types of trials. Industry-sponsored Phase 3 trials were identified from US Food and Drug Administration (FDA) drug approval documentation records.[23] Industry-sponsored Phase 4 trials were identified from the international Clinicaltrials.gov registry maintained by the NIH.[24] NIH-sponsored trials were limited to those administered through the adult AIDS Clinical Trials Group (ACTG), the largest NIH-sponsored HIV trials network, and were identified from the ACTG protocol-specific Web pages.[25] Trials were selected according to the following inclusion and exclusion criteria (Table 1).

All trials—For all categories of trials, we included stand-alone studies of ARV trials in adults (≥12 years old) conducted during or after 1987 (the year in which zidovudine was approved for treatment of HIV). The analysis was limited to trials completed by December 13, 2006 to improve the willingness of pharmaceutical companies to share confidential trial documents.

Phase 3 trials—Industry-sponsored Phase 3 trials were limited to all trials identified as the "pivotal" trials leading to FDA approval of single-formulation HIV medications for adults. The FDA Center for Drug Evaluation and Research (CDER) documents the licensing process for all approved HIV medications and designates specific Phase 3 trials as the "pivotal" sources of data used for approval.[23] Pivotal trials were chosen to create a reasonably sized sample of industry-sponsored trials that spanned nearly 20 years, both before and after introduction of highly active antiretroviral therapy. In addition, all ACTG-administered Phase 3 trials were included.[25]

Phase 4 trials—All industry-sponsored Phase 4 ARV trials registered on Clinicaltrials.gov were included.[24] All ACTG-administered Phase 4 trials were included.

Document Procurement and Data Extraction

We attempted to obtain the protocols and ICFs of all eligible trials. Protocols and ICFs for industry-sponsored trials were obtained by direct request from the sponsoring pharmaceutical companies. Confidentiality agreements were executed between the investigators and all pharmaceutical companies requesting such documentation, ensuring that drugs and trials would be de-identified in all reports. Although we attempted to obtain documents for all remaining trials from the FDA via the Freedom of Information Act, these documents are proprietary and are not subject to this Act (CDER, e-mail communication, Nov. 2, 2006). ACTG protocols and template ICFs were provided by ACTG staff. This research was approved by the Human Subjects Committee of the Massachusetts General Hospital.

Only trials for which complete protocols and ICFs were available by July 1, 2008 (18 months after study initiation) were included. All protocols, appendices, amendments, and template ICFs were reviewed in full by the first author. Missing data were obtained from the ACTG Website and Clinicaltrials.gov when available.

Trial Characteristics and Services Provided to Participants During Trial Periods

Data were collected regarding the date and version number of the last available protocol/amendment, location of trial sites (United States, other developed setting, or resource-limited setting), sponsorship (industry or NIH [ACTG]), anticipated number of participants, age and gender inclusion criteria, and trial duration. Data were also collected regarding additional

services offered to participants during the trial period. These included on-study provision of the study drug itself, other required ARVs ("background regimen"), and substitute drugs (as needed for drug toxicity or virologic failure). We also recorded mention or offer of payment for study participation (worded as "payment," "compensation," or "reimbursement," including offers to compensate subjects for time, transportation costs, or child care costs), and mention or offer of payment for care for trial-related injury. These variables were recorded as comparators for services offered after trial conclusion and in order to test *a priori* hypotheses regarding trial characteristics associated with the primary and secondary outcomes.

Outcomes

The clinical trial was the unit of analysis. The primary outcome was any mention of posttrial services, defined as any text regarding medications or medical care following trial conclusion. Amendments extending the duration of previously enrolled trials met this definition only if they referred to services to be provided after the conclusion of the last described trial phase.

Associations between trial characteristics and the primary outcome were examined using chi-square exact tests with an alpha level of 0.05 (SAS 9.1; SAS Institute, Cary, North Carolina, USA). Multivariate analyses were planned but were precluded by the small sample size. We hypothesized that posttrial services would more frequently be mentioned in the documents of (a) trials with protocols written after 2000 (compared to those written before 2000), reflecting increased awareness of international research ethics guidelines; (b) Phase 3 trials (compared to Phase 4 trials), reflecting a finite period of anticipated need for medications between trial completion and drug licensure; (c) pharmaceutical industry-sponsored trials (compared to NIH/ACTG-sponsored trials), reflecting greater financial resources for provision of posttrial services and 2005 NIH guidelines stating that posttrial medications would not be supplied[15]; (d) trials conducted in developed settings (compared to those conducted in resource-limited settings), reflecting lower levels of anticipated need for posttrial services due to private or public insurance; and (e) trials offering to provide payment for participation or care for trial-related injury during the trial periods (compared to trials not offering such services), reflecting a greater overall willingness to provide services to participants.

For trial documents in which posttrial services were mentioned, secondary outcomes included whether trial documents offered to provide medications or offered to provide medical care to participants after trial completion. If posttrial medications or medical care were offered, information was extracted regarding (a) the type of medications or care offered, (b) which participants were eligible to receive these services, (c) the duration for which these services were offered, and (d) who was to pay for medications or care.

RESULTS

Trial Characteristics and Services Provided to Participants During Trial Periods

Sixty-five trials met criteria for inclusion; documents from 31 of the 65 eligible trials were obtained. Reasons for lack of availability of the remaining documents are detailed in Table 2. Trials ranged widely in number of participants (range, 30–3236; median = 325) and in duration (range, 16–416 weeks; median = 103 weeks) (Table 3). On average, ACTG-administered trials occurred earlier (1987–2004) than industry-sponsored trials (1996–2005). Fifty-eight percent of trials were conducted entirely within the United States, and only two trials (6%) were conducted entirely in resource-limited settings (one each in South Africa and Brazil).

Provision of antiretroviral drugs—During the trial periods, all but one trial offered all necessary study drugs to participants (Table 4). In 16 trials (52%), additional "background" ARVs were required; 6 trials (19%) required participants to obtain these medications from

sources outside of the study, 9 trials (29%) provided background ARVs completely or partially, and 1 trial (3%) did not specify whether background ARVs would be provided. In the event of virologic failure or toxicity requiring substitutions in study drug or background ARVs, three trials (10%) provided any needed substitute ARV; eight trials (26%) provided selected substitute ARVs only; and four trials (13%) stated that substitute ARVs were permitted but not provided. In 15 trials (48%), no substitute ARVs were available, primarily because a need for substitution necessitated study discontinuation.

Mention of payment for study participation—Documents from 23 trials (74%) explicitly mentioned whether participants would be paid for trial participation (Table 4). Eight trials (26% of total trials) specified that participants would be paid, and 15 trials (48% of total trials) stated that participants would not be paid.

Mention of payment for care for trial-related injury—Documents from 29 trials (94%) explicitly mentioned whether participants would receive reimbursement for care for any trial-related injury (Table 4). Seventeen of these (55% of total trials) stated that injury care would be reimbursed, and 12 trials (39% of total trials) stated that such care would not be reimbursed.

Mention and Offer of Posttrial Services

Mention of posttrial services—Posttrial services of any type were mentioned in the documents of 14 trials (45% of trials, 54% of participants; Table 5). Documents from 12 trials (39% of trials, 44% of participants) mentioned posttrial medications. Documents from five trials (16% of trials, 28% of participants) mentioned posttrial medical care. Not mentioning or providing payment to participants, as well as anticipated enrollment greater than the median, were significantly associated with mentioning any posttrial service and with mentioning posttrial medications (Table 6). Enrollment greater than the median, trial sponsor (NIH/ACTG), and not offering payment for injury care (a characteristic of all ACTG trials) were significant correlates of mentioning posttrial medical care.

Offer to provide posttrial medications—Of the 12 trials mentioning posttrial medications, 10 offered to provide medications after trial conclusion (32% of trials, 34% of participants), and 2 stated that posttrial medications would not be provided (6% of trials, 9% of participants). Not mentioning or providing payment to participants, anticipated enrollment greater than the median, and inclusion of at least one trial site in a resource-limited setting were significantly associated with offering to provide posttrial medications. Of the 10 trials offering to provide posttrial medications, 7 were industry-sponsored trials. Seven offered study drug, one offered study drug with background ARVs. Six trials offered posttrial medications to all study completers; two offered posttrial medications only to participants completing the study drug arm. Two additional trials offered the “best available alternative treatment” after trial conclusion (one of these at participant expense), although this was limited to participants failing zidovudine in the late 1980s, when few alternative HIV therapies were available. Six trials offered posttrial medications until commercial availability or for a defined period thereafter, one until a rollover protocol enrolled, and three for an unspecified duration. Posttrial medications were offered at sponsor expense in eight trials, at participant expense in one trial, and without specified payer in one trial.

Offer to provide posttrial medical care—Of the five trials mentioning posttrial care, one (3% of trials, 2% of participants) offered to provide posttrial medical care. This was further explained as the “best available care” for participants failing zidovudine in the late 1980s, offered at participant expense. In the remaining four trials (13% of trials, 26% of participants), documents stated that posttrial care would not be provided.

Trial Characteristics Not Associated with Primary Outcomes

Calendar year of trial documents was not associated with mention of any posttrial service or offer of posttrial medications; 42% of documents from trial documents written before 2000 and 47% of trial documents written after 2000 mentioned any posttrial service ($p = 1.0$). In addition, trial phase (Phase 3 compared to 4), trial duration, age inclusion criteria, and provision of background or substitute ARVs were not associated with mentioning any posttrial service or with offering posttrial care. Because only one trial offered posttrial medical care, bivariate analysis was not performed for this outcome. The small number of trials reviewed precluded multivariate analysis of the associations between trial characteristics and mention or offer of posttrial services.

DISCUSSION

Accurate expectations regarding access to medications and medical care after clinical trial conclusion are crucial to informed decision making by research participants, investigators, and human subjects committee members. This may be particularly true in the case of trials of antiretroviral drugs for HIV infection, after which participants who lack access to effective, combination ARVs may experience clinical deterioration.[11–13] To our knowledge, this study represents the first published review of descriptions of posttrial services in clinical trial documents.

In this sample of major Phase 3 and 4 ARV trials, posttrial medications and medical care were mentioned in the protocols or ICFs of fewer than half (45%) of all trials. Plans regarding payment for trial participation (74%) and payment for care for trial-related injury (94%) were explicitly mentioned more often than were posttrial services, suggesting that authors and reviewers of trial documents are more aware of the importance of describing services offered during trial periods than of the need to outline plans for posttrial services. Posttrial services were mentioned in documents from 12 trials, and 10 (70%) of these offered to provide posttrial medications. Of these 10 trials, 70% were industry-sponsored trials, 60% offered medications until they became commercially available, and 80% offered medications at sponsor expense, reflecting current diversity of recommendations and interpretations about posttrial services.

Decisions about whether posttrial services should be provided are complex, because they include discrete and heavily debated questions about what services should be provided (study medicat ions, other medications, or medical care),[1,10] to whom they should be provided (all study completers, or other community members),[1,26,27] and for how long they should be provided (until medications become commercially available, or indefinitely).[10] Several authors have suggested that trial sponsors should assume at least some responsibility for providing posttrial services.[5,6,16,28] Important roles for investigators, local organizations, and national governments have also been proposed,[6,7,15,28] with or without sponsor financial support to create enduring local health care capacity.[9] The extent of sponsor obligation may depend on whether the sponsor is a government agency or a for-profit entity, which might be expected to have greater financial capacity to provide posttrial services.[27] In support of this concept, the NIH Division of AIDS states that “the NIH’s authority to ‘encourage and support research’ does not extend to providing treatment following the completion of that research.”[15]

We found no association between mention or offer of posttrial services and the year in which trial documents were written (before or after 2000), although our study had limited power to detect such effects. Although research guidelines began to mention posttrial services in the 1990s,[16,21,27] the Declaration of Helsinki (2000, revised 2004) was the first such guideline to clearly recommend that posttrial services be mentioned in trial protocols.[14] Many of the trials included in this review predate these recommendations; however, our limited data suggest that the proportion of trials in which documents mention posttrial services does not appear to have

substantially increased after the year 2000. In 2005, the NIH issued guidelines (quoted above) for trials conducted in resource-limited settings, asserting that NIH would not provide posttrial medications and recommending instead that "investigators engage in a dialogue with host countries' authorities … in order to facilitate the inclusion of [ARV trial participants] in available in-country antiretroviral treatment programs." These guidelines may have increased mention of posttrial services in trial documents; but, by insisting that NIH not provide posttrial medications, they may also have reduced offers of posttrial medications. Documents for the ACTG trials meeting our inclusion criteria were written in 2004 or earlier, and only one was conducted in a resource-limited setting, so these studies were not subject to the 2005 NIH guidelines.

Because of the small numbers of ACTG trials meeting our inclusion criteria, the low proportion of trials provided by pharmaceutical sponsors, and the large number of statistical comparisons made, our conclusions regarding the associations between trial characteristics and mention or offer of posttrial services must be interpreted only as hypothesis-generating. The direction of several statistically significant associations was contrary to what had been hypothesized, for example, mentioning or offering posttrial services was associated with "not mentioning" or "not providing" payment for trial participation, whereas we hypothesized that mentioning or providing payment would suggest a greater overall level of services provided and would be associated with these outcomes. This suggests that other trial factors may explain this association. Similarly, the observed association between not providing injury-related care and mentioning posttrial medical care is explained by a statement common to more recent ACTG trials (1997–2004), specifying that pediatric and pregnancy-related care would not be provided if participants became pregnant during the studies. Numbers of included trials were too small to permit multivariate analysis to further explore these relationships.

Major international research ethics guidelines do not provide specific guidance to researchers regarding posttrial services.[14,16,17,19–21] It is likely that no single recommendation about posttrial services will be appropriate to all research situations, because the specific risks to participants and needs of the communities in which research is conducted will differ between trials.[2] Instead, it may be helpful to outline a process by which posttrial services can be included among the other risks and benefits considered in the standardized evaluation of all proposed trials.[2] For example, education regarding posttrial services could be a component of the training required for a Federal-Wide Assurance (FWA) number for human subjects committees.[29] Additionally, a description of "planned post-trial services" could be added as a required component of trial protocols and ICFs. This might involve a requirement similar to that currently in place for trials that are subject to FDA requirements and that involve at least minimal risk to subjects: ICFs for such trials must include clear descriptions of plans regarding payment for care for trial-related injury, regardless of whether or not such payment will be provided.[9,14,30]

During the protocol development process, sponsors may be appropriately reluctant to commit to a future obligation to provide posttrial services, due to uncertainty about drug efficacy or about future financial circumstances.[18,19,31] However, given the very high expectations of some surveyed trial participants, [1,10] a statement about posttrial services, even one that makes explicit that posttrial services are not guaranteed, may help to ensure that unreasonable expectations do not play a role in decisions about trial participation.

This study has several important limitations. First, documents other than protocols and ICFs (including internal memoranda, sponsor/investigator contracts, and local ICFs) may contain information about posttrial services and were not reviewed in this study. However, with the exception of local ICFs, these additional documents are likely to be less readily available to participants, investigators, and site human subjects committee members than the protocols and

template ICFs. Second, we reviewed all available versions of protocols and ICFs, and the definition of "mention of post-trial services" was fulfilled only if such mention referred to the time after the trial period described in that document version was to conclude. Although this definition may incompletely capture the practice in which trial sponsors provide posttrial services through amendments that extend trials until drugs become commercially available, it is consistent with the goal of making planned posttrial services explicit at the time of participant recruitment.

Finally, the eligible sample of 65 ARV trials included only pivotal industry-sponsored Phase 3 trials leading to medication licensure, rather than complete sample of Phase 3 ARV trials, and included only ACTG-administered trials, rather than all NIH-sponsored trials. Furthermore, the obtained sample included fewer than half of the eligible trials (93% of ACTG trials, but only 34% of industry-sponsored trials).

This sample of reviewed trials may be biased for two reasons. First, the inclusion of only "pivotal" Phase 3 industry-sponsored trials (those leading to medication approval) resulted in a sample of trials of efficacious medications, after which sponsors may be more likely to offer medications than after trials of inefficacious medications. Second, sponsors may have been less willing to share eligible trial documents in which posttrial services were not mentioned. If documents from all 34 unavailable trials did not mention posttrial services, then the total proportion of trials mentioning post services could be as low as 14 of 65 (22%) overall: 47% (7/15) of ACTG studies and (14% 7/50) of industry studies. Both sources of bias would be expected to lead to results indicating that posttrial services are mentioned or offered more frequently than is really the case. Although clearly important limitations of our study, these factors may suggest that the low frequencies of the outcomes that we observed are even more worthy of consideration.

We are aware of no reports of actual rates of receipt of posttrial services by trial participants with HIV infection or other medical conditions. Efforts to characterize trial participants' expectations regarding posttrial services and their actual rates of receipt of such services remain important directions for future research. In the meantime, trial sponsors should explicitly communicate their plans about posttrial services to trial participants, investigators, and human subjects committees at the time of protocol approval and participant recruitment, whether or not they intend to provide such services. This could be accomplished by including clear descriptions of plans for posttrial services in trial protocols and informed consent forms. This review suggests that such explicit statements are not yet the standard practice in major HIV clinical trials.

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Table 1

Identification of clinical trials eligible for review

Trial category	Data sources and inclusion and exclusion criteria
All trial categories	Trials of single-formulation antiretroviral drugs (ARVs) for HIV infection (substudies, pharmacokinetic studies, and studies of fixed-dose combination medications[a] excluded) Completed between Jan. 1, 1987 and Dec. 13, 2006[b] Trials in adults (age ≥12 years)
Industry-sponsored Phase 3 trials	Designated by FDA CDER as a "pivotal" trial leading to FDA approval of a single-formulation ARV
Industry-sponsored Phase 4 trials	Registered with Clinicaltrials.gov Industry sponsorship (alone or in combination with government or academic sponsors)
ACTG-administered trials	Registered with ACTG online protocol-specific web pages Phase 3 or 4 (trials designated as "Phase 2/3" by the ACTG website were included if designated as Phase 3 by the trial protocols and by Clinicaltrials.gov)

Note: ARV = antiretroviral drug; FDA = United States Food and Drug Administration; CDER = Center for Drug Evaluation and Research.; ACTG = AIDS Clinical Trials Group.

[a] Trials of fixed-dose combination medications were excluded because these medications do not require separate Phase 3 trials for approval.

[b] Completed trials were selected in different ways for each trial category, as required by the different data sources. For industry-sponsored Phase 3 trials, those completed and leading to drug licensure by Dec. 13, 2006 were included. For industry-sponsored Phase 4 trials, trials designated by Clinicaltrials.gov as "no longer recruiting patients" were selected, and search results were reviewed by hand to include only studies designated as "completed" or "terminated" by Dec. 13, 2006. In order to identify ACTG-administered trials conducted in a similar time period to industry-sponsored trials, ACTG trials designated as "completed," "closed to follow-up," or "partial off-study/partial analysis completed" by Dec. 13, 2006 were included.

Table 2

Trial eligibility and document procurement

Trial type	Number of trials identified	Number of trials obtained	Number of trials and status of missing documents
Industry, Phase 3	34[a,b]	10	6 – Companies declined to participate (2 companies) 3 – Company provided only excerpts of ICFs (1 company) 10 – Confidentiality agreement pending as of July, 2008 4 – Protocols or ICFs could not be located by company
Industry, Phase 4	17	7	5 – Companies declined to participate (2 companies) 3 – Confidentiality agreement pending as of July 2008 2 – Protocols or ICFs could not be located by company
ACTG, Phase 3	14[b]	13	1 – Archived ICF not available (19 years after study conclusion)
ACTG, Phase 4	1	1	n/a
Total	**65*b***	**31**	**34**

Note: ICF = informed consent form; ACTG = AIDS Clinical Trials Group.

[a] FDA documentation was complete for 17 of 24 approved medications in December 2006.

[b] One Phase 3 trial was sponsored by both the NIH/ACTG and a pharmaceutical company; it was identifi ed among both the Industry, Phase 3 and the 14 ACTG, Phase 3 trials. For analysis, this trial was included with the ACTG trials, leaving 33 eligible Industry, Phase 3 trials.

Table 3

Characteristics of antiretroviral trials included in systematic review

Trial characteristics	All	ACTG		Industry	
		Phase 3	Phase 4	Phase 3	Phase 4
Total	31	13	1	10	7
Planned enrollment					
Range (*n*)	30–3,236	30–3,236	285	210–660	40–400
Total (*n*)	16,270	10,477	285	4,278	1,230
Median (*n*)	325	538	285	513	135
≤325, no. of trials (no. of participants)	16 (2,895)	5	1	5	5
>325, no. of trials (no. of participants)	15 (13,375)	8	0	5	2
Age requirements, *n* (%) trials					
≥12–17 years old	24 (77%)	10 (77%)	1 (100%)	8 (80%)	5 (71%)
≥18 years old	7 (23%)	3 (23%)	0	2 (20%)	2 (29%)
Gender, *n* (%) trials					
Women and men	30 (97%)	12 (92%)	1 (100%)	10 (100%)	7 (100%)
Men only	1 (3%)	1 (8%)	0	0	0
Protocol date, range	1987–2004	1987–2004	2002	1997–2005	1996–2004
Study duration, weeks[a]					
Range	16–416	24–206	416	56–154	16–103
Median	103	142	—	102	54
Study sites, *n* (%) trials[b]					
US only	18 (58%)	10 (77%)	1 (100%)	3 (30%)	4 (57%)
US and other developed	5 (16%)	2 (15%)	0	2 (20%)	1 (14%)
Non-US developed	3 (10%)	0	0	1 (10%)	2 (29%)
US and resource-limited setting	2 (7%)	1 (8%)	0	1 (10%)	0

Note: ACTG = AIDS Clinical Trials Group.

[a] Trial duration was defined as the longest possible duration for any single participant, including screening, study, and follow-up phases.

[b] Data regarding trial site are missing for three trials.

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Table 4

Services provided to antiretroviral trial participants during the study periods

	All		ACTG		Industry	
	Trials(%)	**Participants(%)**	**Phase 3**	**Phase 4**	**Phase 3**	**Phase 4**
Total	31	16,270	13	1	10	7
Study medications provided						
Entirely provided	30 (97%)	15,495 (95%)	12 (92%)	1 (100%)	10 (100%)	7 (100%)
Partially provided	1 (3%)	775 (5%)	1 (8%)	0	0	0
Other required ARVs provided						
Not provided	6 (19%)	1,890 (12%)	0	1 (100%)	2 (20%)	3 (43%)
Completely/partially provided	9 (29%)	3,288 (20%)	1 (8%)	0	7 (70%)	1 (14%)
Not specified	1 (3%)	325 (2%)	0	0	0	1 (14%)
No other required ARVs	15 (48%)	10,767 (66%)	12 (92%)	0	1 (10%)	2 (29%)
Substitute ARVs provided						
Not provided	4 (13%)	1,385 (9%)	0	0	3 (30%)	1 (14%)
All substitutes provided	3 (10%)	2,860 (18%)	2 (15%)	0	1 (10%)	0
Select substitutes provided	8 (26%)	4,302 (26%)	4 (31%)	0	3 (30%)	1 (14%)
No substitutes available	15 (48%)	7,438 (46%)	7 (54%)	0	3 (30%)	5 (71%)
Not mentioned	1 (3%)	285 (2%)	0	1 (100%)	0	0
Payment for trial participation						
Provided	8 (26%)	1,530 (9%)	1 (8%)	0	2 (20%)	5 (71%)
Not provided	15 (48%)	8,336 (51%)	6 (46%)	1 (100%)	6 (60%)	2 (29%)
Not mentioned	8 (26%)	6,404 (39%)	6 (46%)	0	2 (20%)	0
Payment for care for trial-related injury						
Provided	17 (55%)	5,508 (34%)	0	0	10 (100%)	7 (100%)
Not provided	12 (39%)	7,335 (45%)	11 (85%)	1 (100%)	0	0
Not mentioned	2 (6%)	3,427 (21%)	2 (15%)	0	0	0

Note: ACTG = AIDS Clinical Trials Group; ARV = antiretrovirals.

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Table 5

Descriptions of posttrial services in protocols and informed consent forms of major antiretroviral trials

	All		ACTG		Industry	
	Trials	**Participants**	**Phase 3**	**Phase 4**	**Phase 3**	**Phase 4**
Of 31 trials reviewed	**31**	**16,270**	**13**	**1**	**10**	**7**
Mention any posttrial service	14 (45%)	8,747 (54%)	7 (54%)	0	5 (50%)	2 (29%)
In protocol	9 (29%)	5,550 (34%)	1 (8%)	0	5 (50%)	2 (29%)
In consent	10 (32%)	6,712 (41%)	6 (46%)	0	2 (20%)	1 (14%)
Mention posttrial medications	12 (39%)	7,105 (44%)	5 (38%)	0	5 (50%)	2 (29%)
In protocol	8 (26%)	5,235 (32%)	1 (8%)	0	5 (50%)	2 (29%)
In consent	7 (23%)	3,320 (20%)	4 (31%)	0	2 (20%)	1 (14%)
Offer to provide medications	10 (32%)	5,580 (34%)	3 (23%)	0	5 (50%)	2 (29%)
Medications NOT provided	2 (6%)	1,525 (9%)	2 (15%)	0	0	0
Mention posttrial medical care	5 (16%)	4,482 (28%)	5 (38%)	0	0	0
In protocol	1 (3%)	315 (2%)	1 (8%)	0	0	0
In consent	5 (16%)	4,482 (28%)	5 (38%)	0	0	0
Offer to provide care	1 (3%)	315 (2%)	1 (8%)[a]	0	0	0
State care NOT provided	4 (13%)	4,167 (26%)	4 (31%)	0	0	0
Of 10 trials offering medications:	**10 (32%)**	**5,580 (34%)**	**3 (23%)**	**0**	**5 (50%)**	**2 (29%)**
Type of medication						
Study drug	7 (70%)	3,485 (21%)	0	—	5 (100%)	2 (100%)
Study drug + background ARVs	1 (10%)	1,750 (11%)	1 (33%)	—	0	0
"Best available treatment"[b]	2 (20%)	95 (<1%)	2 (67%)	—	0	0
Participants eligible						
All completers	6 (60%)	4,075 (25%)	1 (33%)	—	3 (60%)	2 (100%)
All completers, study drug	2 (20%)	1,160 (7%)	0	—	2 (40%)	0
All failing study drug[b]	2 (20%)	95 (<1%)	2 (67%)	—	0	0
Duration of medication						
Until commercial availability	6 (60%)	3,160 (19%)	0	—	5 (100%)	1 (50%)
Until rollover protocol enrolls	1 (10%)	1,750 (11%)	1 (33%)	—	0	0
Not specified	3 (30%)	670 (4%)	2 (67%)	—	0	1 (50%)
Who will pay for medications						
Trial sponsor	8 (80%)	5,235 (32%)	1 (33%)	—	5 (100%)	2 (100%)
Not specified	1 (10%)	31 (<1%)	1 (33%)	—	0	0
Participants[b]	1 (10%)	95 (<1%)	1 (33%)	—	0	0

Note: ACTG = AIDS Clinical Trials Group; ARVs = antiretrovirals.

[a] Care provided at participant expense.

[b] "Best available alternative" to zidovudine for those failing zidovudine in late 1980s; one or two trials offered at participant expense.

Table 6

Trial characteristics associated with mention or offer of posttrial services: Bivariate analysis

	Total	Mention any posttrial service (*n* = 14)			Mention posttrial medications (*n* = 12)			Offer posttrial medications (*n* = 10)			Mention posttrial medical care (*n* = 5)	
	N	N	%p	N	%	p	N	%p	N	%p	N	%p
Sponsor			0.72			1.00		0.22		0.012		
NIH (ACTG)	14	7	50	5	36		3	21	5	36		
Industry	17	7	41	7	41		7	41	0	0		
Phase			0.24			0.43		0.57		0.29		
Phase 3	23	12	52	10	44		8	35	5	22		
Phase 4	8	2	25	2	25		2	25	0	0		
Site			0.20			0.14		0.045		0.30		
Non-RLS	29	12	41	10	36		9	31	4	14		
RLS + Dev'd	2	2	100	2	100		1	50	1	50		
Protocol year			1.00			1.00		1.00		1.00		
1987–99	12	5	42	5	42		4	33	2	17		
2000–05	19	9	47	7	37		6	32	3	16		
Trial duration			1.00			0.48		0.18		0.63		
≤2 years	18	8	44	8	44		8	44	2	11		
>2 years	13	6	46	4	31		2	15	3	23		
Age			0.41			0.68		1.00		0.31		
≥12	24	12	50	10	42		8	33	5	21		
≥18	7	2	29	2	29		2	29	0	0		
Planned enrollment			0.004			0.029		0.038		0.017		
≤325	16	3	19	3	19		3	19	1	6		
>325	15	11	73	9	60		7	47	4	27		
Other required ARVs			0.80			0.79		0.64		0.088		
Completely/partially provided	9	3	33	3	33		3	33	0	0		
Not provided	6	3	50	3	50		3	50	0	0		
Not specified/not applicable	16	8	50	6	38		4	25	5	31		
Substitute ARVs			0.25			0.84		0.95		0.19		
All substitutes provided	3	1	33	1	33		1	33	1	33		
Select substitutes provided	8	6	75	4	50		3	38	3	38		
Not provided	4	2	50	2	50		2	50	0	0		
Not mentioned/not applicable	16	1	33	5	31		4	38	1	6		
Injury care payment			0.40			0.72		0.28		0.026		
Yes	17	7	41	7	41		7	41	0	0		
No	12	7	58	5	42		3	25	5	42		
Not specified	2	0	0	0	0		0	0	0	0		
Payment for participation			0.014			0.023		0.009		0.48		
Yes	8	0	0	0	0		0	0	0	0		
No	15	9	60	7	47		7	47	3	20		
Not mentioned	8	5	63	5	63		3	38	2	25		

Note: NIH = National Institutes of Health; RLS = resource-limited setting; Dev'd = developed-country setting; ARVs = antiretrovirals.

* *p*-values are for comparisons using trial as the unit of analysis in chi-square exact tests. All *p*-values for comparisons using participant as the unit of analysis were statistically signifi cant, with $p < 0.001$.