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AIDS Clinical Trials Group Longitudinal Linked Randomized Trials (ALLRT): Rationale, Design, and Baseline Characteristics

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Abstract

Purpose—ALLRT is a longitudinal cohort study of HIV-infected subjects prospectively randomized into selected clinical trials for antiretroviral (ARV) treatment-naïve and ARV treatment-experienced individuals conducted by the AIDS Clinical Trials Group (ACTG). We describe the rationale, design, and baseline characteristics of the ALLRT cohort and its potential to address important research questions related to ARV therapy.

Method—Standardized visits occur every 16 weeks to evaluate long-term clinical, virologic, and immunologic outcomes associated with ARV treatment.

Results—A total of 4,371 subjects enrolled in ALLRT from January 2000 through June 2007. Of these, 3,146 (72%) were ARV naïve at parent study entry (18% female, 44% white, 32% black, 21% Hispanic; median age 37 years, CD4 count 218 cells/μL, follow-up 3.6 years; 343 [11%] followed ≥8 years) and 1,225 (28%) were treatment experienced (13% female, 59% white, 20% black, 17% Hispanic; median age 42 years, CD4 count 325 cells/μL, follow-up 5.7 years).

Conclusions—ALLRT provides the opportunity to understand long-term ramifications of therapeutic ARV choices and determine whether these vary by treatment regimen, timing of treatment initiation, or treatment changes over long-term follow-up. Investigations based on uniform data and specimen collection in the context of randomized ARV treatments will be critical to developing more successful long-term therapeutic strategies for HIV treatment.

Keywords

CD4 counts; cohort studies; epidemiologic research design; HIV; randomized controlled trials; viral load

Since its inception in 1987, the AIDS Clinical Trials Group (ACTG) has performed clinical trials in persons with human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) focused on measuring the impact of antiretroviral (ARV) therapies, treatment strategies, prophylaxis and treatment of opportunistic complications, and immune-based interventions on HIV disease morbidity and survival. These studies have had significant influence in determining appropriate management for HIV disease and its

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complications, contributing to our understanding of HIV pathogenesis and, in many cases, providing critical information useful in development and use of novel agents and establishing standards of care.[1–11] Results from ACTG and other studies have provided new insights into HIV pathogenesis, availability of better tools for monitoring viral replication and resistance to ARV drugs in vitro and in vivo, and the availability of a wider array of better tolerated and more convenient potent ARV drugs and drug regimens that have drastically improved management of HIV disease.[12–15] As a consequence, research priorities and the structure of clinical trials have required substantial modification in focus and scope.

Short-term fixed-regimen, fixed-duration comparative trials for defined patient populations are important to characterize the comparative antiviral activity of drugs and regimens and novel treatment strategies, but they often do not address long-term management questions in an efficient and generalizable manner. One approach to characterize longer term outcomes is to prospectively plan meta-analyses or cross-protocol analyses of longitudinally followed subjects who undergo standardized collection of information about treatment regimens, factors that impact treatment response, and outcomes over an extended time period. The ALLRT study provides the context in which the ACTG can examine longer term outcomes among subjects who have participated in their shorter term fixed-duration trials.

METHOD

Overview and Design of the ACTG Longitudinal Linked Randomized Trials (ALLRT) Protocol

The ALLRT study (protocol A5001) is a unique prospective cohort consisting of subjects participating in United States-based ACTG clinical trials who have been randomly assigned to ARV therapies, immune-based therapies, or strategies for anti-HIV interventions. The primary aim is to determine long-term (5 years or longer) virologic, immunologic, pharmacologic, and clinical outcomes and complications associated with therapeutic interventions. The protocol is designed with flexibility to incorporate evolving scientific aims and allow additional questions to be addressed as knowledge and HIV management issues change over time. Investigators conduct analyses using clinical, laboratory, and subject self-reported data and use state-of-the-art laboratory techniques to perform testing on stored specimens. The majority of ALLRT subjects have also provided samples for the assessment of host genetic factors related to ALLRT outcomes.[16] In its current protocol version, ALLRT will enroll approximately 4,500 subjects and is designed to continue following subjects through year 2010; sample size will be increased in updated versions of the protocol to allow for entry from ACTG clinical trials with novel or contemporary treatment regimens.

Study Population

Subjects aged 13 years or older with documented HIV-1 infection at all stages of HIV disease are eligible to enroll in ALLRT if they are enrolled in an approved parent ACTG clinical trial that provides a randomized treatment intervention and agree to participate in this longitudinal observational study. Major exclusions to participation include factors that would compromise the ability to comply with scheduled study visits and long-term follow-up. Some parent clinical trials were enrolling subjects before ALLRT initiated enrollment in the year 2000. For subjects in these clinical trials, there were the additional criteria that the subjects had to be alive and not lost to follow-up in the year 2000. Subjects provide written informed consent. Each ACTG study site received approval from their designated institutional review board (IRB) prior to protocol initiation.

To date, 25 ACTG clinical trials have served as parent studies from which ALLRT subjects have been recruited (Table 1). Seven parent studies enrolled subjects who were ARV treatment naïve or had limited prior exposure to nucleoside reverse transcriptase inhibitors and 18

enrolled ARV treatment-experienced subjects. ACTG protocols that provide randomized ARV treatment, immune-based therapies, or strategies for anti-HIV interventions with the potential to contribute to ALLRT objectives were approved as parent studies. In addition, these trials had a follow-up time of at least 24 weeks and had the potential to be combined with at least one other study with a similar initial treatment/strategy. Six ACTG studies were not selected to be included as ALLRT parent studies; one due to a primary objective other than ARV treatment outcomes and five due to the lack of comparable treatment arms within the studies that could contribute to cross-protocol comparisons.

Site staff and outreach personnel have a variety of methods for recruiting subjects to ACTG studies (i.e., parent clinical trials). Methods used include referrals from local care providers, recruitment from their own local or affiliated clinics, advertising, community forums, and recruiting events; sites are expected to recruit a diverse population reflective of the epidemic in their location. A variety of retention strategies are also employed including provision of facilities or payment for transportation, child care, food, or reimbursement for study visits, all within National Institutes of Health (NIH), Office for Human Protections (OHRP), and IRB allowable guidelines. It was site procedure to approach all eligible subjects in the parent studies to enroll into ALLRT.

Prospective follow-up begins when a subject enters his/her parent study and continues within the context of the parent protocol until that study closes, an endpoint is reached, or the subject's parent protocol participation otherwise ends. During the time a subject is on the parent study, data are collected for the parent study and additional data elements are collected for ALLRT; once the patient's participation in the parent study ends, follow-up and data collection continues according to the ALLRT schedule. If a subject enrolls sequentially in more than one ALLRT parent study, baseline is considered the date of entry into the subject's earliest parent study. Subjects may subsequently enroll in additional ACTG or other clinical trials and continue participation in the ALLRT protocol. The ALLRT protocol allows for data collection from other sources after parent study participation has ended, provided there is adequate source documentation. Data from non-ACTG laboratories are accepted for inclusion if the testing lab is Clinical Laboratory Improvement Amendments (CLIA)-certified or the equivalent.

Data Collection

Timing of ALLRT evaluations is linked to the parent protocol entry visit, which is considered the "baseline" visit. Baseline visits occur prior to the start of parent study treatment, providing an opportunity to examine pretreatment characteristics among ARV-naïve subjects. ALLRT subjects are seen every 16 weeks for a standardized assessment. Every 48 weeks, subjects also complete a health and medication adherence self-report and undergo a neurological screening evaluation. Every 96 weeks, blood is drawn for hepatitis serology testing. Whenever possible, ALLRT makes use of data collected in parent protocols to minimize blood collected, study visit length, and costs and to reduce complexity for subjects and ACTG clinic personnel. Study site staff record data using standard case report forms and enter these data into the ACTG database. Data are maintained at the ACTG Data Management Center, where data range, code versus text, and logical checks are conducted. In addition, site visits are conducted by a study monitoring team to perform data quality assurance checks for subsets of all ACTG protocols, and each site is required to have a formal quality assurance program through which site personnel perform quality assurance checks on all data before data entry and for all data queries and responses.

At the ACTG Statistical and Data Analysis Center, a standardized computer program extracts data from the ALLRT protocol database as well as those of ACTG parent and co-enrolled studies. ALLRT data are assessed by programmers, statisticians, and epidemiologists,

assembled into a yearly derived dataset in preparation for analyses, and are periodically reviewed by clinician-investigator members of the core protocol team.

Medical Events

Information on HIV-related diagnoses and AIDS-defining events are obtained from subjects every 16 weeks. In addition, data about conditions possibly related to complications of HIV and its therapies, including body fat distribution abnormalities/lipodystrophy (buffalo hump, lipomas, central [trunk] fat accumulation, facial/limb fat loss), diabetes mellitus, myocardial infarction, stroke, hypertension, and hepatic or renal dysfunction, are collected. Women enrolled in ALLRT provide information on the date of their last menstrual period and hysterectomy and/or menopause status (if applicable). ALLRT also obtains information on past and current smoking status and individual and family cardiovascular history (cardiovascular disease, myocardial infarction, and sudden death prior to age 55 or 65 in primary male or female blood relatives, respectively). Gynecologic history is updated every 48 weeks, and family cardiovascular history is updated every 96 weeks.

Mortality data are reported on ALLRT. Primary cause of death must be assessed by a physician; site staff request the death certificate and pertinent hospital or outpatient records in addition to other source documentation, and these are used to determine the cause of death. If the death certificate, medical record information, or other source documentation is not available on a subject who is known to have died, the cause of death is recorded as “unknown.” The ACTG does not search the National Death Index.

Medication

ARV and immune-based anti-HIV medication use and/or regimen changes are self-reported by the subjects every 16 weeks; history of use is obtained for subjects who are ARV experienced at baseline. Regimen changes of less than 21 days duration are not reported in ALLRT. In keeping with the long-term goal to obtain information on HIV disease progression, ALLRT also collects data about therapies for prophylaxis, maintenance, and treatment of opportunistic infections and HIV-related malignancies. Other medications targeted in ALLRT include lipid-lowering therapies, hormonal therapies (oral contraceptives, hormone replacement therapy, selective receptor modulator therapies), and therapies for body fat distribution abnormalities/lipodystrophy. Specific treatment is not provided through the ALLRT protocol but is provided/managed by the parent protocols; after the parent study is complete, ALLRT subjects may establish their treatment regimen with their treating physician.

Clinical Assessment

Weight, vital signs (blood pressure, temperature, and pulse), and standardized body measurements (hip, mid-waist, and mid-arm circumference) are assessed at ALLRT entry and every 16 weeks; height is measured at baseline. Clinicians conduct a physical exam targeted at current symptoms/signs; symptoms/signs at or above grade 3, as outlined in the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (2004),[17] are recorded on case report forms. Prior to the updated release, ALLRT used the DAIDS Table for Grading Severity of Adult Adverse Experiences (1992).[18]

A brief battery of neurologic screening tests is administered at ALLRT entry and repeated every 48 weeks. The tests include a standardized peripheral neuropathy screening tool, Trail Making Test, Parts A and B,[19] and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol Test.[20] Information about demographics, including age, educational level, and primary language, is collected. This neurological screening examination has been validated as a tool to detect neurologic and cognitive dysfunction in HIV-infected persons in ALLRT.[21]

A pelvic exam, including a Pap smear, is performed on women every 48 weeks. Subjects also self-report on medication adherence (number of doses missed in past 4 days, how closely the subject followed dosing instructions), quality of life (number of days spent in bed and cut down on daily activities, working status, health status), and medical resource utilization (number of nights spent in the hospital, number of trips to the emergency department) every 48 weeks.

Laboratory Evaluations

Nadir (lowest CD4 absolute count prior to entering the study) and every 16-week CD4+ T-cell counts as well as pretherapy and every 16-week plasma HIV-1 RNA results are obtained. CD4 results for ALLRT are obtained from CLIA-certified (or equivalent) local laboratories. All ALLRT evaluations of HIV-1 RNA levels use the Ultrasensitive Roche Amplicor Monitor assay (Roche Molecular Systems, Inc., Branchburg, New Jersey, USA); the majority are performed at the ACTG central testing laboratory located at The Johns Hopkins University and the results are transmitted electronically to the Data Management Center. In addition, ALLRT collects data on hematologic, hepatic and renal function, glucose, lipids, and a quantitative urinalysis (urine protein, creatinine) every 16 weeks; specimen testing is completed at local laboratories. From January 2000 to June 2003, ALLRT also collected information on naïve and memory CD4 subsets and CD8 activation. Serologic tests for hepatitis A, hepatitis B, and hepatitis C are completed at ALLRT entry and repeated every 96 weeks.

Plasma, serum, and frozen and viable peripheral blood mononuclear cell (PBMCs) aliquots are prepared and subsequently stored in a central repository for later use in investigator-driven research. In addition, the majority (>85%) of ALLRT subjects have consented to store and use DNA specimen samples to examine host genetic factors and other HIV-related genetic testing.[16]

RESULTS

Demographics and ACTG Parent Entry Clinical Descriptors

Between January 2000 and June 2007, 4,371 subjects enrolled in ALLRT (Table 2). There were 7,539 subjects enrolled in the ACTG parent studies of which 7,079 (94%) were eligible to enroll in ALLRT; 62% of those eligible were subsequently enrolled. Those considered not eligible included subjects who were off-study or died prior to January 2000 and subjects who were participating at sites not in the United States. Seventy-two percent (n = 3,146) of ALLRT subjects were ARV naïve when they entered their ACTG parent study and 28% (n = 1,225) were ARV treatment experienced. Overall, the majority of ALLRT subjects are male (ARV naïve, 82%; ARV experienced, 87%) and more women were ARV naïve than ARV experienced (18% vs. 13%) at parent study entry. Overall, half of the subjects are non-white (ARV naïve, 56%; ARV experienced, 41%), and the racial distribution of ARV-experienced and ARV-naïve subjects differs significantly ($p < .001$, chi-square test). ARV-experienced subjects were older than ARV-naïve subjects when they entered their parent studies (median age 42 years old vs. 37 years old; $p < .001$, Wilcoxon rank sum test; Table 2). Ten percent of subjects had a history of injection drug use at parent study entry. Overall distribution of CD4+ T-cell counts at parent entry differs between the ARV-naïve and the ARV-experienced subjects ($p < .001$, chi-square test). Notably, 21% of the ARV-naïve group and only 5% of the ARV treatment-experienced group had a baseline CD4+ T-cell count ≤ 50 cells/μL, and 9% of the ARV-naïve group and 27% of the ARV treatment–experienced group had a baseline CD4+ T-cell count >500 cells/μL. Median baseline CD4+ T-cell count was 218 cells/μL in the naïve group and 325 cells/μL in the experienced group. As expected, the majority of the ARV treatment-experienced group had an HIV-1 RNA viral load ≤10,000 copies/mL at parent entry (58%), while the majority of ARV-naïve subjects had HIV-1 RNA viral loads >10,000 copies/mL (89%).

Overall, the majority of subjects on ALLRT started a parent study randomized regimen/strategy that included a protease inhibitor (PI; 35%) or non-nucleoside reverse transcriptase inhibitor (NNRTI; 31%), and two nucleoside reverse transcriptase inhibitors (NRTIs) (Table 3). Subjects with a history of ARV use prior to entering their parent study were most likely to be randomized to a PI and NRTI regimen (56%). Approximately 98% of all subjects took at least three ARVs when entering their parent study.

ALLRT follow-up begins when subjects enter their parent study; 35% entered their parent study from 1997 to 1999, 24% entered from 2000 to 2002, and 41% entered from 2003 to date. Over time, the proportion of ARV-naïve black enrollees increased from 28% in 1997–1999 to 33% from 2003–2007; correspondingly, the proportion of white enrollees decreased from 47% to 42% in the same time period. In addition, there was a slight increase in the percentage of ARV-naïve subjects under age 25 entering between 1997–1999 (5%) and 2003–2007 (7%). Other subject demographic characteristics remained fairly stable over time (data not shown).

Among ARV treatment-naïve subjects from parent studies where final analyses have been completed, pretreatment characteristics are fairly similar for subjects who chose to enroll in ALLRT (n = 1,616, 64%) versus those who chose not to enroll in ALLRT (n = 891, 36%). Subjects in ALLRT versus those not in ALLRT were not statistically different for baseline CD4+ count (median: 215 vs. 201, $p = 0.37$), baseline HIV RNA (88,000 vs. 102,000, $p = 0.45$), or sex (19% vs. 17% female, $p = 0.32$). While meeting statistical significance ($p < 0.001$), age was not considerably different (median: 37 vs. 36 years). Race, however, was statistically different ($p < .0001$), with 45% white and 31% black subjects enrolling in ALLRT, whereas the subjects who chose not to enroll in ALLRT were 33% white and 46% black. Additionally, the proportion of subjects entering ALLRT did not differ significantly by randomized treatment arm ($p \geq .08$ for completed studies with ARV-naïve subjects).

Of the 4,371 subjects enrolled in ALLRT, 74% (n = 3,252) are active participants in the cohort in the year 2007. Median follow-up time per subject, starting at parent entry, is 3.6 years for the ARV-naïve subjects (maximum 10.3 years) and 5.7 years for the ARV-experienced subjects (maximum 10.3 years). ARV-naïve (n = 672, 21%) and treatment-experienced subjects (n = 268, 22%) who have been lost to follow-up contributed an average of 3.1 and 4.1 years to the study, respectively. Subjects lost to follow-up are those who have discontinued the study for any reason other than death; subjects who have missed three consecutive ALLRT clinic visits without reasonable cause are discontinued from the study, although they may rejoin. In the first year after enrolling into ALLRT, 4% of subjects are lost to follow-up; overall, the loss to follow-up rate is 5.8 per 100 person-years. Approximately 4% of subjects enrolled in ALLRT are lost to follow-up either on or before the date they go off their parent study; of those lost to follow-up after their parent study ends, approximately 60% remain on ALLRT for at least 1 year after parent trial completion. Subjects lost to follow-up were younger (median age 37 years) than the overall cohort (median age 39 years). Other baseline demographic factors (sex, race, CD4+ count, HIV viral load, injection drug use) were similar between those subjects who remain on study and those lost to follow-up. For subjects on study throughout an entire calendar year, the percent who completed three clinic visits varied between 73% and 89% (2001, 89%; 2002, 87%; 2003, 84%; 2004, 84%; 2005, 79%; 2006, 73%). There have been 179 (4%) deaths reported on ALLRT, of which 89 (50%) were among ARV-naïve subjects. Among ARV-naïve subjects, 14 (16%) deaths were HIV-associated, 40 (45%) were non-HIV associated, 18 (20%) were accidental/other, and 17 (19%) were reported as reason unknown. Among subjects who were ARV treatment-experienced when they entered their parent study, 30 (33%) deaths were HIV-associated, 40 (44%) were non-HIV associated, 7 (8%) were accidental/other, and 13 (14%) were reported as reason unknown.

DISCUSSION

ALLRT is a unique cohort, which includes over 4,300 subjects enrolled from a variety of ACTG clinical trials in which treatment is randomly assigned and subjects are prospectively followed for an extended period after the original randomized clinical trial ends. The ALLRT cohort consists of ARV treatment-experienced and treatment-naïve subjects with a range of demographic characteristics (sex, age, race/ethnicity, injection drug use) and pretreatment CD4 + T-cell counts and HIV-1 RNA levels. Such variety, among a large cohort followed long term, offers interested ACTG-affiliated investigators and collaborators the opportunity to examine treatment issues among subgroups and uncommon endpoints and to address interrelated correlates of disease progression or ARV-related complications. This is not feasible in single studies of finite duration. In addition, if outside investigators propose analyses they wish to perform using ALLRT data, we pair them with an ACTG-affiliated investigator or ALLRT protocol team member to assist with logistics (statistical, data systems, policies and procedures).

The standardized protocol used in the ALLRT cohort offers an advantage over typical clinic-based cohorts. In ALLRT, visits are every 16 weeks, and prespecified clinical, laboratory, and self-reported factors are collected in real time on standardized clinical event forms, while specimens are collected and stored for future testing. In contrast, in clinic-based cohorts, HIV-infected individuals may be seen when they are sick rather than on a regular schedule, or intervals between regularly scheduled visits may vary substantially. When subjects are seen, data collection is typically not uniform across all subjects, therefore missing data points may be more frequent. Analyses generally utilize medical records.[22] Irregular visit intervals and variable data collection may lessen the strength of some clinic-based cohort analyses, whereas ALLRT has the advantage not only of initial randomization to treatment interventions among ARV-naïve subjects but also of rigorous standardization of data collection.

Aspects of the ALLRT protocol present additional advantages over other study designs. For example, ALLRT has a more diverse population than a single-site cohort, making the findings more generally applicable. Collaborative cohort studies that use large numbers of subjects in their analyses do not have the same level of detail in their data, such as specific start and stop dates for ARV use. ALLRT also has study visits every 16 weeks; this interval tends to be shorter than that seen in other interval cohort studies. Another key value of ALLRT is the availability of specimen and DNA repositories, and the linkage of defined clinical and laboratory data from patients with a longitudinal specimen repository and DNA repository.

Even though other cohorts, such as the MACS,[23] WIHS,[24] and ALIVE,[25] also follow standardized protocols and data collection, ALLRT has the distinction of enrolling subjects who were randomized to ARV treatment interventions. By using cross-protocol and cross-treatment arm analyses from the ALLRT protocol, in the context of parent study randomized initial ARV treatment regimens, strategies, and approaches to management of toxicities, the compounded levels of bias introduced when clinicians or subjects individually select initial and subsequent treatments or thresholds for switching treatments may be avoided, thus decreasing the impact of confounding by initial regimen selection. Assessing the influence of pre-ARV treatment factors on responses to ARV treatment is complicated by the possibility that the ARV regimen selected for an individual may be driven by pretreatment factors of interest. For example, if more potent regimens are given to individuals with low CD4+ cell counts, the relationship between pretreatment factors such as CD4+ cell count and outcomes may be confounded by the ARV regimen selected. Removing this treatment bias among the ARV-naïve subjects who enter ALLRT provides results that may be more broadly generalizable than might be achieved by analyzing retrospective or purely observational cohorts or single randomized clinical trials.[26,27] Reduced bias associated with randomization

may not extend to the ARV-experienced patient population in this study, because their first ARV regimen was prior to enrollment in their parent study. For this reason, some analyses are restricted to the ARV-naïve population. In addition, ongoing longitudinal and time-to-event analyses are based on data from the parent studies, including non-ALLRT subjects, combined with the additional long-term follow-up within ALLRT and use analytic approaches such as inverse probability of censoring weighting[28,29] to address potential selection bias for subjects contributing long-term follow-up data.

ALLRT also provides an opportunity to address questions related to cardiovascular and renal events, neurologic complications, malignancies, AIDS-related events, and death. A number of ALLRT data elements used in analyses to address these questions are not routinely collected in HIV cohort studies. For example, based on the neurologic screening assessments, lower nadir CD4+ counts were associated with neurocognitive impairment.[30] Another longitudinal analysis of ALLRT demonstrated an association between HIV viral suppression (after starting an initial or new ARV treatment) and improved renal function among subjects with baseline renal function impairment and low CD4+ counts.[31]

Although ALLRT offers a rich dataset, there are some limitations. Many clinic-based cohorts retain all HIV-infected individuals who come to clinic for care throughout their lifetime. In ALLRT, subjects choose to enroll in an ACTG clinical trial, thus narrowing the group of HIV-infected individuals followed and decreasing the generalizability of the findings to the entire HIV-infected population. In addition, subjects may go off study when their health begins to decline, thus diminishing the ability of ALLRT to capture endpoints that occur after a subject becomes increasingly sick. In an attempt to continue data collection in this situation, ALLRT encourages continued follow-up of such patients by allowing for use of clinical data from medical records if subjects are no longer able to comply with study visits; ALLRT also collects mortality data.

The course of complications in patients for whom potent ARV therapy has failed is unknown. The ALLRT cohort provides an opportunity to examine the clinical course and predictors for development of complications and to address long-term management and preventive strategies. To assess susceptibility to virologic breakthrough, disease progression, and the degree to which immune reconstitution is possible when viral replication is suppressed with treatment, long-term evaluation that focuses on measures of general immunity (cellular activation, maturation, function) and HIV-specific and opportunistic pathogen-specific immunity will be required. In addition, the interrelationships among these components of host immunity, as well as their correlation with established markers of HIV prognosis (i.e., HIV-1 RNA and absolute CD4+ T-cell count) require further study. This can be accomplished in the context of long-term follow-up in ALLRT and testing available serum, plasma, PBMC, and DNA specimens that have been collected as part of the study. For example, in one study using DNA specimens derived from ALLRT subjects, polymorphisms in genes encoding TRAIL, TNF-α, Bim, IL-15, and IL-15 receptor α chain were associated with magnitude of CD4+ cell increase following initiation of ARV treatment, as were haplotypes in genes encoding IFN-α, Il-2, and IL-15 receptor α chain ($p < .05$ for each).[32] Data for the study were hypothesis-generating and are being used to further explore the multiple genetic variants that may influence immune recovery following initiation of ARV therapy.

CONCLUSION

The ALLRT population is a diverse group of HIV-infected individuals who entered ACTG clinical trials at various stages of infection and have maintained relationships with their ACTG clinics over the long-term, providing abundant valuable information on the course and complications of HIV in the era of potent ARV therapy. For example, efavirenz plus two

NRTIs,[15] one of the regimens recommended as standard of care for initial ARV treatment in most treatment guidelines, was an initial randomized regimen in multiple ALLRT parent studies, and ALLRT now has 8-plus years of follow-up data for the earliest parent studies using this regimen. Performing longitudinal measurements in a cohort the size of the ALLRT will make it possible to evaluate the role of a range of factors, including age, sex and race, as well as genetic determinants that may affect the occurrence and manifestations of various abnormalities and complications associated with HIV disease and its therapies. With a median follow-up to date of 4 years, this cohort provides a rich source of data for analyses across many specific HIV subject areas. As a unique cohort, ALLRT fills a niche to address key long-term scientific questions important for the HIV treatment research community.

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Table 1

Parent studies enrolled into ALLRT, by antiretroviral status at entry into parent study

Parent study	Study title	Sample size	Study duration (median follow-up)	Reference
Studies enrolling ARV-naïve subjects				
384	PI ± NNRTI w/Dual Nucleosides in Initial HIV Therapy	980	2.3 years	Robbins et al., 2003[8] and Shafer et al., 2003[7]
A5014	Cellular Dynamics & Immune Restoration w/NVP+LPV/r or 3 NRTIs (d4T/3TC/ABC)	55	48 weeks	Landay et al., 2003[33]
A5095	Comparison of 3 PI-Sparing Regimens for Initial HIV Treatment	1148	2.8 years	Gulick et al., 2004[10] and 2006[11]
A5142	LPV/r + EFV vs. LPV/r + 2 NRTIs vs. EFV + 2 NRTIs for Initial HIV Therapy	757	2.2 years	Riddler et al., 2006[34] and Haubrich et al., 2007[35]
A5202	EFV or ATV/r Combined with FTC/TDF or ABC/3TC in Naive Subjects	1591	Ongoing [subjects will participate for approximately 96 weeks beyond enrollment of last subject]	No publication available.
347	Phase II of APV Monotherapy vs. APV+ZDV+3TC in HIV	92	28 weeks	Murphy et al., 1999[36]
388	EFV or NFV + Fixed-Dose Combination 3TC/ZDV+IDV	517	2.1 years	Fischl et al., 2003[37]
Studies enrolling ARV-experienced subjects				
364	Virologic Efficacy of NFV ± EFV + 2 Nucleosides	237	2.8 years	Albrecht et al., 2001[6]
372A	Prolongation of Virologic Success in Subjects Receiving IDV+NRTIs	229	5.3 years	Hammer et al., 2004[38]
373	APV+3TC+ZDV (d4T) vs. IDV +NVP+3TC+d4T vs. other Treatments in APV-Experienced Patients	79	2.7 years	Gulick et al., 2001[39]
398	APV+PI (3 arms) or APV +ABC/EFV/Adefovir in PI-Experienced Subjects w/Viral Failure	481	1.2 years	Hammer et al., 2002[40]
400	Salvage Therapies for NFV Treatment Failures	25	46 weeks	No publication available.
A5024	Potent ART, HIV Immunization & IL-2 Cycles to Control Viral Replication	81	1.4 years	Kilby et al., 2006[41]
A5025	Safety & Efficacy of Hydroxyurea in Patients with VL < 400 on ART	207	1.1 years	Havlir et al., 2001[42]
A5057	Effect of Immunogen Vaccine on Time to Virologic Relapse in Patients on ART	160	48 weeks	No publication available.
A5064	Early Treatment Intensification of ART	16	36 weeks	Bartlett et al., 2003[43]
A5068	Intermittent ART Interruption and Double-Blinded Immunization with ALVAC-	97	2.1 years	Jacobson et al., 2006[44]

Parent study	Study title	Sample size	Study duration (median follow-up)	Reference
	HIV vCP1452 in Patients with Virologic Success and CD4 >400			
A5076	Sequencing vs. Phenotyping Resistance Testing Among Patients with ARV Failure	84	45 weeks	No publication available.
A5110	Thymidine Analogue Substitute or Change to an NRTI-Sparing Regimen for Peripheral Fat Wasting	106	1 year	Murphy et al., 2006[45]
A5115	ART Switch at Lower vs. Higher Viral Load in Patients with Viral Relapse on Current HAART Regimen	47	1.6 years	Riddler et al., 2007[46]
A5126	Predictive Value of PK-Adjusted Phenotype Susceptibility on Response to PIs/r in Patients with Prior PI Failure	53	24 weeks	Eron et al., 2006[47]
A5135	Fixed-Dose vs. Concentration-Adjusted LPV/RTV in Patients on Salvage Therapy	4	28 weeks	No publication available.
A5143	LPV/r vs. fAPV+ RTV vs. LPV/r+ fAPV+ TDF + 1 or 2 NRTIs in Patients with Virologic Failure	56	37 weeks	Collier et al., 2005[48]
A5146	Effect of TDM on Viral Response to Salvage Regimen in Patients with NIQ ≤1 to 1 or More PIs	411	45 weeks	Demeter et al., 2008[49]
A5211	Safety/Efficacy of Adding Vicroviroc to Patients Failing ART regimen (Including RTV)	118	Ongoing 48 weeks; additional 4 years of safety visits	Wilkin et al., 2007[50] and Gulick et al., 2007[51]

Note: ARV = antiretroviral; PI = protease inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; NVP = nevirapine; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; d4T = stavudine; 3TC = lamivudine; ABC = abacavir; EFV = efavirenz; ACTG = AIDS Clinical Trials Group; ATV/r = atazanavir with ritonavir; FTC = emtricitabine; TDF = tenofovir; APV = amprenavir; ZDV = zidovudine; NFV = nelfinavir; IDV = indinavir; RNA = ribonucleic acid; CROI = Conference on Retroviruses and Opportunistic Infections; AIDS = acquired immune deficiency syndrome; ART = antiretroviral therapy; IL-2 = interleukin-2; VL = viral load; CD4 = cluster of differentiation 4; HAART = highly active antiretroviral therapy; PK = pharmacokinetic; fAPV = fosamprenavir; RTV = ritonavir; DF = disoproxil fumarate; TDM = therapeutic drug monitoring; NIQ = normalized inhibitory quotient; CCR5 = chemokine receptor 5.

Table 2

Demographics and ACTG parent entry clinical descriptors of subjects enrolled in ALLRT as of June 30, 2007 (*N* = 4,371)

		ARV-naïve (*n* = 3,146, 72%)		ARV-experienced (*n* = 1,225, 28%)		Overall (*N* = 4,371)	
Baseline characteristic		***n***	**%**	***n***	**%**	***n***	**%**
Sex	Male	2574	82	1070	87	3644	83
	Female	572	18	155	13	727	17
Race/Ethnicity	White	1378	44	725	59	2103	48
	Black	1007	32	249	20	1256	29
	Hispanic	667	21	212	17	879	20
	Asian	61	2	19	2	80	2
	Native American/Alaskan	13	0	15	1	28	1
	Other	16	1	5	0	21	0
	Missing	4	0	0	0	4	0
Age, years	Median (Q1–Q3)	37 (31–44)		42 (37–48)		39 (33–45)	
	≤24	210	7	19	2	229	5
	25–34	962	31	178	15	1140	26
	35–44	1240	39	542	44	1782	41
	45–54	566	18	381	31	947	22
	55–64	147	5	99	8	246	6
	≥65	21	1	6	0	27	1
Injection drug use	Ever	273	9	144	12	417	10
	Never	2873	91	1081	88	3954	90
CD4, cells/μL	Median (Q1–Q3)	218 (71–344)		325 (181–533)		243 (103–389)	
	≤50	663	21	65	5	728	17
	51–200	805	26	285	23	1090	25
	201–350	924	29	324	26	1248	29
	351–500	472	15	215	18	687	16
	>500	280	9	335	27	615	14
	Missing	2	0	1	0	3	0
HIV RNA, copy/mL	Median (Q1–Q3)	60,000 (24,000–234,000)		4,000 (140–34,000)		42,000 (11,000–164,000)	
	≤10,000	349	11	709	58	1058	24
	>10,000–100,000	1581	50	356	29	1937	44

Baseline characteristic		ARV-naïve (*n* = 3,146, 72%)		ARV-experienced (*n* = 1,225, 28%)		Overall (*N* = 4,371)	
		n	**%**	***n***	**%**	***n***	**%**
	>100,000	1216	39	159	13	1375	31
	Missing	0	0	1	0	1	0
Follow-up time, years	Median (Q1–Q3)	3.6 (1.3–5.6)		5.7 (3.1–8.6)		4.0 (1.6–6.4)	

Table 3

Parent study regimens for ALLRT subjects by ARV experience at parent study entry (*N*=3,413)

	ARV-naïve (*n* = 2,188)		ARV-experienced (*n* = 1,225)		All (*N* = 3,413)	
ARV drug class[a]	***n***	**%**	***n***	**%**	***n***	**%**
Did not start ARVs	4	<1	4	<1	4	<1
PI only	12	1	15	1	27	1
NRTI only	273	12	41	3	314	9
PI+NRTI	502	23	686	56	1188	35
PI+NNRTI	208	10	22	2	230	7
NRTI+NNRTI	909	42	148	12	1057	31
PI+NRTI+NNRTI	280	13	313	26	593	17
Number of ARVs[b]						
0	4	<1	0	0	4	<1
1	12	1	14	1	26	1
2	0	0	15	1	15	<1
3	1367	62	526	43	1893	55
4	805	37	317	26	1122	33
≥5	0	0	353	29	353	10

Note: Subjects in ACTG clinical trials where parent study ARV regimens are still blinded to the study team are excluded. ARV = antiretroviral; PI = protease inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor.

[a] More than one drug could be included in the same drug class.

[b] Subjects taking one ARV were on the monotherapy arm of ACTG 347; subsequently, all were moved onto a ≥3 drug regimen. Ritonavir is counted as a separate ARV (even at low dose). Kaletra is counted as two ARVs.