

## **Section 1: Executive Summary from the Group Leadership**

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In keeping with our work of the past 16 years, the Adult AIDS Clinical Trials Group (AACTG) has progressed through another year of record accomplishments in the investigation of therapeutic interventions for the treatment of HIV-1 disease, the prevention and treatment of HIV/AIDS-related opportunistic diseases and complications of therapy, and of the viral and immune pathogenesis of HIV-1 and its complications. This has been a year of immense challenges coupled with critically important accomplishments, met and achieved in an environment of increasingly difficult budget constraints and broadly shifting research priorities and opportunities. In this past year, the AACTG has embraced with enthusiasm its ongoing responsibilities and mission, and with the development of our collaborative International Clinical Trials initiatives we are poised to make new contributions, modeled on our previous successes but enhanced with innovation in the international arena, that we hope will have a lasting impact on progress toward ending the HIV/AIDS epidemic.

The scientific updates in Section 3 of this report provide a comprehensive summary of AACTG accomplishments of the past year, but we wish to particularly highlight several of the major scientific and administrative achievements.

### **MAJOR SCIENTIFIC ACCOMPLISHMENTS OF 2003**

#### **New findings further defining effective strategies for initial therapy of HIV-1 disease, with a notable impact on the standard of care:**

- The combination of zidovudine, lamivudine, and efavirenz is the most potent and effective of the currently available regimens studied for initial therapy. – This was first established by ACTG 384 and confirmed by A5095. These data are now incorporated into all domestic and international treatment guidelines. Data from ACTG 384 are in press in two manuscripts to be published in the *New England Journal of Medicine*. Data from ACTG 5095 was presented at the 2<sup>nd</sup> IAS Conference on HIV Pathogenesis and Treatment in Paris, July 2003, and a manuscript is under review.
- The combination of three nucleosides (zidovudine, lamivudine, and abacavir) is inferior to efavirenz + nucleosides as initial therapy. – This was convincingly demonstrated in A5095. The clear and highly statistically significant results of A5095 do not preclude the use of three nucleosides in specific settings or for specific individuals, but they do require a significant increase in justification for use as an initial treatment strategy. These data have also been incorporated into national and international treatment guidelines.
- Potent combination antiretroviral therapy used in initial treatment of HIV-1 infection has a durable effect and does not require intensification over time (ACTG 372A – a 5-year strategy study).

- Initial therapy with four drugs is not superior to three, provided the initial three-drug regimen is potent (ACTG 384, ACTG 388). – Data generated by these studies have also been incorporated into national and international treatment guidelines.

**New findings demonstrating the increased complexity of and for individualization of treatment options in the management of antiretroviral treatment failure:**

- Minor NNRTI-resistant variants, which are often missed by standard genotyping, contribute to treatment failure of EFV (and likely other NNRTI) based regimens (ACTG 398). – This analysis of ACTG 398 is critical in our understanding of treatment failure in patients who are treatment-experienced, and may have enormous implications for the international mother-to-child-transmission (MTCT) effort.
- Early virologic failure is associated almost exclusively with 3TC resistance when the initial regimen contains a protease inhibitor with 3TC and a second nucleoside (ACTG 388). – This information confirms earlier studies, provides a roadmap for determining one of the major resistance pathways likely to be followed by the virus under drug selection pressure, and contributes to our understanding of how to individualize subsequent treatment regimens for patients who fail their initial therapy.
- Two ACTG studies showed that didanosine (ddl) retains antiviral activity in the presence of the M184V mutation induced by lamivudine (ACTG 307, ACTG 364). – As a result of these studies, resistance interpretation algorithms and guidelines for managing treatment failure in the setting of drug resistance have been changed.
- The presence of efavirenz hypersusceptibility appears to enhance virological responses during treatment with efavirenz in combination with nucleoside analogs (ACTG 364 and 398).
- Resistance of HIV-1 to ARV agents is a continuum of declining activity over a defined range of IC<sub>50</sub> or fold-change for a given drug and is probably better conceptualized as gradient of reduced susceptibility (ACTG 359, ACTG 398). – The further refinement of this concept by the data generated in AACTG studies illustrate that simplistic approaches (all or none) to interpretation of drug resistance or management of treatment failure are misleading.

**New findings related to the immunopathogenesis of immune recovery or reconstitution following treatment with potent antiviral regimens:**

- After 6 years of potent ART only one third of patients who started treatment with moderately advanced immunosuppression achieve normal CD4+ T-cell counts or recover T cell function (ACTG 315/375). – These data have major implications for determining the most appropriate time to initiate antiretroviral therapy, and suggest that those who start with more advanced immunosuppression are unlikely to experience a timely recovery of immune function, and, indeed, may never fully recover normal immune function.

- Older (> 45 y.o.) HIV-1-infected individuals have reduced naïve T-cell responses, which are associated with reduced survival rather than production of naïve T cells (A5015). These data, too, have an impact on the decision regarding when to start ART and suggest that individualized approaches to this decision may be necessary based on the underlying characteristics of the patient.
- Immune restoration following initiation of ART is not dependent on the mechanism of drug activity, and that PI-containing regimens do not provide additional early immunologic benefit independent of their antiviral activity when compared to PI-sparing regimens (A5014). – These data support the findings described above related to the choice of initial therapy for HIV-1-infected individuals.

**Expansion of our knowledge of sex/gender differences in responses to antiretroviral therapies:**

- HIV-1-infected women treated with a saquinavir-based regimen had improved virological responses as compared to men, and this improved response was associated with higher concentrations of saquinavir in women (ACTG 359). – These data further support the continued exploration of differences in weight and pharmacokinetic parameters in women and men as determinants of antiviral response.
- Women appear to have lower exposure to efavirenz compared to men, independent of body-mass index (BMI), but there do not appear to be sex differences in the pharmacokinetics of nelfinavir or indinavir; however, BMI significantly affects the area-under-the-concentration curve (AUC) of both of these drugs (DACS 215).

**New findings related to the management of chronic HCV infection in HIV-1 co-infected patients:**

- While chronic hepatitis C due to genotypes 2 and 3 in HIV-1 coinfecting individuals responds equally well to the current standard of treatment for mono-infected patients (pegylated interferon plus weight-based dosing of ribavirin), the response in HIV-1 co-infected patients with HCV genotype 1 is substantially worse, and may be so poor that this therapy should generally not be offered (A5071). A5071 is the first major study, and the largest randomized controlled trial to be completed of treatment for chronic HCV infection in HIV-1 coinfecting individuals. These results have changed the standard of care for HIV/HCV coinfecting individuals, and have clearly demonstrated the compelling need for new approaches and novel therapy for this devastating coinfection.

**New findings related to the assessment and treatment of metabolic, body fat, and other complications of antiretroviral therapies:**

- The combination of zidovudine, lamivudine, and efavirenz is less likely than other potent regimens to be associated with metabolic and body fat composition changes (ACTG 384, A5005s).

- Current commonly used lipid-lowering agents (statins and fibrates) rarely lower lipids to NCEP-recommended levels in HIV-1-infected persons with severe dyslipidemia, even when they are used in combination (A5087). – These data have altered the current approach to the management of dyslipidemia in HIV-1-infected patients, and as with other findings reported this year by the AACTG, illustrate the need for further investigation of new approaches and novel therapies to reduce the metabolic consequences of current ARV drugs.
- Both efavirenz and nelfinavir, potent inducers of CYP 3A4, significantly reduce drug exposure to pravastatin when used in combination (A5108). – This study provides additional insights into how HMG CoA reductase inhibitors are affected by commonly used antiretroviral drugs that induce their metabolism, and suggest that when treatment for lipid abnormalities is necessary in HIV-1-infected patients being treated with these antiretroviral drugs, the dose of pravastatin required may be substantially higher than previously anticipated. These data may also partially explain the poor overall response to statins seen in A5087.
- Contrary to previously published information, hyperlactatemia is a very rare phenomenon (when lactate levels are measured carefully), and asymptomatic elevations are most often transient and clinically insignificant (A5099, A5129). – These data have been incorporated into national and international treatment guidelines and support the cost-savings recommendation that routine monitoring of lactate levels in patients receiving nucleoside analogues should not be performed.
- Efavirenz neurotoxicity is predominantly vestibular, short lived, and does not compromise overall improvement in neurocognitive function observed following the initiation of antiretroviral therapy (A5097s).

#### **Improvements in the management of opportunistic infections:**

- HIV-1-infected patients with CD4+ T cell counts less than 50 cells/ $\mu$ L and detectable CMV viremia are at high risk for development of CMV end-organ disease; pre-emptive treatment should be considered in this setting (ACTG 360). – This study was a challenging one to complete due to the dramatic declines in opportunistic infections following the widespread use of potent combination ART, however, perseverance paid off and the results of this study clearly demonstrate that for those patient who do not benefit immunologically from ART, there may be other interventions that can identify and treat those at risk to prevent a devastating opportunistic complication of HIV-1 disease.
- Suppressive maintenance therapy for disseminated MAC, CMV, and histoplasmosis can safely be withdrawn after immune reconstitution on antiretroviral therapy to CD4+ T-cell levels above the recognized threshold of risk for these opportunistic infections (ACTG 379, ACTG 393, A5038).

#### **MAJOR INTERNATIONAL THERAPEUTIC RESEARCH ACCOMPLISHMENTS FOR 2003**

- International clinical trials units (ICTUs) have been established in 12 locations around the world including South Africa, Malawi, Zimbabwe, India, Thailand, Haiti, Brazil, and Peru, and have been partnered with U.S. ACTUs. Together with the HIV Prevention Trials Network (HPTN) three regional training programs were conducted, with curricula focused on instruction in the management of antiretroviral therapy and its complications, opportunistic infections, clinical trials conduct, ethics, GCP and GLP, as well as budget and administrative planning in preparation for conducting. Site, laboratory, protocol, and AACTG procedure-specific training for international investigators and staff have proceeded in-country and at U.S. ACTUs.
- HPTN 052 and A5175, the first two therapeutic protocols to be conducted jointly at 8 of the 12 sites, have completed protocol development, nearly completed negotiations for clinical trials drug supply, and are nearing final versions to be submitted to local IRBs for review and approval. Site assessment and implementation visits are being conducted, with the intent to open A5175 in the first quarter of 2004.
- The University of Witwatersrand ICTU in Johannesburg, South Africa, has enrolled 5 subjects in A5073, an AACTG study evaluating the impact of directly observed therapy on virologic outcome of antiretroviral treatment. This is the first AACTG clinical trial to be opened at an ICTU located in an international resource-limited site. The ICTU located at the Nelson Mandela School of Medicine in Durban, South Africa, is poised to enroll its first patients in A5142 in November 2003.
- Through a participatory and iterative process driven by the research needs of the international investigators, a prioritized international scientific agenda has been developed, and concept proposals are being considered to address major components of that agenda.
- The AACTG Executive Committee (AEC) has opened the nomination process for new investigators to join the Executive Committee, SASC, RACs, Scientific and Resource Committees to international investigators and staff, with the intent of fully integrating investigators from international sites into all levels of the AACTG.
- The AACTG has embarked on an ambitious path to more effectively coordinate and collaborate with other NIAID/DAIDS-funded networks. Current efforts underway include: 1) the collaboration with the HPTN in the design and conduct of HPTN 052 and A5175; 2) a collaboration with the PACTG and HPTN to jointly develop and conduct A5190 to evaluate the safety and toxicity of antiretroviral drugs in infants born to mothers who have been treated during pregnancy while participating in HPTN 052 and A5175; 3) joint participation in a working group led by the HVTN and the NIH Intramural Vaccine Research Center (VRC) to harmonize laboratory techniques for the study of HIV-1-specific immunity in the context of vaccine trials in seropositive and seronegative persons; 4) a collaboration with the VRC to study a candidate vaccine construct in individuals with chronic HIV-1 infection; 5) a collaboration with the Acute Infection and Early Disease Research Program (AIEDRP) to explore therapeutic intervention studies of persons with acute or early HIV-1 infection.

- In planning for future international initiatives, the AACTG leadership has also surveyed AACTG investigators to develop an inventory of international collaborations that can be built upon to expand NIAID international therapeutic clinical trials programs in key locations, including the 14 “Bush initiative” countries, the Caribbean basin, and in China. As resources become available, international therapeutic clinical trials may be expanded to include many of these areas as sites are developed in collaboration with other NIAID/DAIDS-supported networks or investigators.

### **MAJOR ADMINISTRATIVE ACCOMPLISHMENTS FOR 2003**

The AEC continues to diligently oversee the Group’s Core funds to determine that they are used in the most effective manner to strengthen the productivity of the Group. As NIH/NIAID budgets face new constraints, and as the therapeutic research needs stretch to encompass the international community, particularly in resource-limited areas of the world, the AEC, in collaboration with the SASC, RACs, Scientific Committees, other major resource committees, and the principal investigators of the AACTG, worked proactively and vigorously in 2003 to examine both the Group’s scientific agenda and the resources and costs associated with supporting that agenda. The AEC and SASC reviewed the current financial commitments of the Group with the goal of achieving a more focused set of research and administrative priorities. Understanding the budgetary limitations on the Group, the Group leadership worked closely with the AACTG Operations Center to review the obligated expenses in the Central Group budget to determine where cost savings might occur, while ensuring that adequate operational funds and support personnel continued to be available to maintain the overall vitality and mission of the Group. These scientific agenda prioritization and operational funding reviews have led to the following decisions:

- Site costs related to performance of what are now routine diagnostic tests or assays will be assumed as part of research protocol costs supported by ACTU site budgets rather than Central Group discretionary funds, freeing up those funds for high priority initiatives.
- The AACTG will complete its current portfolio of studies on metabolic bone changes in the coming year, but will not develop new protocols in this area, since the current studies are believed to be adequate to answer the salient research questions.
- A re-evaluation of the number of advanced flow cytometry and lymphoproliferative assays required for protocols investigating immunopathogenesis questions has concluded that most of these protocols have met their objectives; these assays will now be limited in number and scope to pre-defined subsets of patients enrolled in a small number of future protocols, reducing the need for costly laboratory support.
- Fee for Service (FFS) immunology laboratories, i.e., local laboratories performing immunology assays for AACTG protocols, will no longer be supported (with the exception of those in Hawaii and Puerto Rico for logistical reasons), as the need for real-time advanced flow cytometry and lymphoproliferative assays for a large number of AACTG protocols has been eliminated; the remaining work will be accommodated in the Immunology Support Laboratory system.

- A number of poorly or slowly accruing protocols were re-evaluated and were 1) closed (A5102, A5135, A5141, A5149); 2) redesigned and the sample size and complexity reduced (A5146, A5126, 5179); subjected to closer monitoring and additional performance timelines in anticipation of possible early closure (A5115, A5165, A5082, A5110, ACTG 736, A5127). Laboratory expenses committed to these protocols have been or will be instead committed to other protocols, projects or functions of the Group.
- After careful review by the RACs, a number of secondary and tertiary objectives within ongoing protocols were re-prioritized within the context of the shifting research opportunities available. A number of these objectives will not be included in protocol analyses, and Central Group funds supporting them will be withdrawn. In studies where external support from sponsors has been provided to fund their performance, testing and analyses will continue.
- The review of new concept proposals has been centralized within the SASC, with stricter criteria in place for approval of new proposals for protocol development.
- A comprehensive re-evaluation of the Group's domestic scientific agenda has been conducted by the SASC with the end result being the elimination of several lines of investigation for which the Group has determined 1) there are already studies in progress within the AACTG to address them in a definitive manner; 2) there are insufficient patient populations or opportunities to adequately address them at this time; 3) they are of lower priority than other more pressing research needs; 4) the research questions involved have already been or are being actively investigated by other groups such that further work by the AACTG will be duplicative and have less impact. This re-examination has resulted in a compression of the domestic scope of work planned by the Group.
- Limitations have been placed on the number of conference call participants, and the number, frequency, and length of routine conference calls to conserve funds.
- The AEC, SASC, and RACs conducted an in-depth review of the proliferating number of focus and working groups within the AACTG and have streamlined the organizational structure which, in turn, will further decrease the conference call costs and the level of Operations Center support necessary for these groups.
- The Operations Center staff conducted a thorough review of all contracts requiring funds from the Central Group budget, and closed those contracts that were no longer appropriate allowing funds to be redirected to other priorities of the Group.
- The AEC decided to undertake an internal re-competition of the Support Laboratories to 1) stimulate increased laboratory creativity and encourage renewed enthusiasm; 2) facilitate more overt demonstration of accountability, productivity, and value added to the Group; 3) potentially attract new investigators to the Group; 4) set the stage for the laboratory component of the competitive renewal and facilitate development of a more coordinated and integrated laboratory agenda for the Group; and 5) establish a stable laboratory infrastructure to support laboratory research in hepatitis B and C, international laboratory investigation, and genomics projects, and to integrate these into the Support Laboratory

infrastructure. The solicitation was issued in August and applications were submitted by October 3, 2003. The review process is underway.

- Much work has been done to explore and remove barriers to recruitment and retention of underrepresented minorities in AACTG trials, although further efforts are needed in several areas. Overall, recruitment of women has increased by 4.2%, African American subjects by 8.2%, Hispanic subjects by 3.4%, Asian/Pacific Islander subjects by 1.5%, and Native American subjects by 0.5% compared to the previous year. Recruitment rates for IDUs have remained stable at 12.9% of overall study subjects.
- The Community Constituency Group (CCG) expanded its working relationship with the domestic ACTU Community Advisory Boards (CABs), broadened its responsibilities in pre-reviewing draft protocols to determine their applicability to community constituents and to address community issues related to individual studies. The CCG is participating in the development of A5175, and is exploring mechanisms and opportunities to assist the international sites in their development of effective CABs.

## **FUTURE DIRECTIONS**

In the next grant year, the AACTG will begin preparing for a recompetition of the Group at a critical juncture in the future of HIV/AIDS therapeutic research. During this time, we must continue the work that has led to the many successes we now enjoy in the developed world. The AACTG will continue to develop and conduct studies of new or novel antiretroviral drugs, regimens, and strategies that will tell us how to further enhance our ability to treat our patients in the U.S. and in resource-limited countries to achieve long-term maximal suppression of HIV-1 replication in infected individuals with 1) the least toxicity; 2) the most clinically effective immunologic reconstitution; 3) the greatest long-term benefit, and; 4) the most impact in reducing the morbidity and mortality associated with HIV-1 disease.

Principal goals for the coming year will be 1) to efficiently and successfully complete and publish the high-priority studies described in Section 3; 2) to bring more novel compounds into the AACTG and test more novel strategies to achieve the goals described above; 3) to complete high-impact projects evaluating genetic mechanisms or the role of genetic factors in the pathogenesis of HIV-1 disease, of ART-associated metabolic complications, and the immunologic and virologic responses to therapy; 4) to study novel strategies to treat and prevent the complications of HIV/AIDS and its therapies; 5) in collaboration with international investigators, to implement and complete accrual to A5175 and HPTN 052; 6) to develop and implement protocols to address the high-priority scientific questions posed in the international scientific agenda developed by our ICTU colleagues; 7) to forge successful collaborations with other NIAID/DAIDS funded networks to more efficiently use resources, particularly in resource-limited international settings; 8) to explore additional interactions with international colleagues in China, the 14 countries named in President Bush's HIV/AIDS initiative, and in the Caribbean basin; and 9) continue the process of technology transfer, development, and enhancement of infrastructure and capacity building in international resource-limited settings. These current and future activities will maintain our long-standing tradition of excellence in therapeutic clinical investigation of HIV-1 disease, and allow us

further opportunities to contribute to improving the health and lives of persons living with HIV/AIDS throughout the world.

On behalf of the AACTG leadership, we again wish to express our gratitude and commend all of our investigators, research staff, and other support personnel at all of our AACTUs, our ICTUs, at the Operations Center, the Statistical and Data Analysis Center, the Data Management Center, and the Division of AIDS for your ongoing efforts, professionalism, excellence, enthusiasm, and support of the AACTG and the work that we do. We look forward to another stimulating and rewarding year in our goal to end the HIV/AIDS epidemic.

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