



PARTNER PROJECT AGREEMENT #G-2103p

BETWEEN

THE INTERNATIONAL SCIENCE AND TECHNOLOGY CENTER,

**THE NATIONAL CENTER FOR DISEASE CONTROL AND PUBLIC HEALTH
OF GEORGIA**

AND

**THE DEPARTMENT OF HEALTH AND HUMAN SERVICES
OF THE UNITED STATES OF AMERICA**

Patterns of HIV drug resistance and molecular epidemiology of HIV in Georgia

Operative Commencement Date: February 1, 2014

2. A handwritten signature in blue ink, appearing to be 'S. Smith'.

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Definitions

"Agreement" means an ISTC project agreement

"Party" means a Party to the Agreement Establishing an International Science and Technology Center

"Financing Party" means a Party providing funds for an ISTC project (The United States Department of Health and Human Services through the BTEP program);

"Partner" means an organization that has been approved by the ISTC Governing Board to participate in the ISTC Partner Program on a regular basis (The U.S. Department of Health and Human Services) and acts as an ISTC partner;

"Recipient" means an organization of the Russian Federation or other country of the former Soviet Union, which conducts work under an ISTC project agreement

The International Science and Technology Center (hereinafter referred to as "**the Center**"), the National Center for Disease Control and Public Health of Georgia (hereinafter referred to as "**the Recipient**"), and the U.S. Department of Health and Human Services, National Institute of Health/National Institute of Allergy and Infectious Diseases (NIH/NIAD) (hereinafter referred to as the "**Partner**"), represented for the purpose of the signature of this Project Agreement (hereinafter referred to as "**the Agreement**") by their authorized representatives (with the Center, the Recipient, and the Partner hereinafter referred to collectively as "**the Signatory Parties**"),

TAKING INTO ACCOUNT THE FOLLOWING CONSIDERATIONS:

The United States of America, Japan, the Russian Federation and, acting as one Party, the European Atomic Energy Community and the European Community (with these two organizations hereinafter referred to as "**the European Community**") signed the Agreement Establishing the International Science and Technology Center on November 27, 1992 (hereinafter referred to as "**the ISTC Agreement**") and the Protocol on Provisional Application of the Agreement Establishing the International Science and Technology Center on December 27, 1993 (hereinafter referred to as "**the ISTC Protocol**"),

The Republic of Georgia, the Republic of Armenia, the Republic of Belarus, the Republic of Kazakhstan, the Kyrgyz Republic, Norway, the Republic of Korea, the Republic of Tajikistan and Canada have acceded, and additional States may accede, to the ISTC Agreement and to the ISTC Protocol to participate in the activities of the Center,

The Center is a legal entity and has been registered by the Ministry of Foreign Affairs of the Russian Federation as an international organization with its headquarters in Moscow,

The Recipient is a legal entity within the Republic of Georgia,

The Partner, established as a U.S. Federal Department under U.S. law and having its principal office in Washington, DC, is a legal entity that has been approved by the Center's Governing Board to participate in Center activities as an ISTC Partner, in accordance with the Memorandum of Agreement between ISTC and DHHS signed on July 6, 1999 and August 10, 1999.

The Governing Board of the Center has approved a project to be funded by the Partner through the Center in the domain covered by the Agreement concerning cooperation in approved projects in the health sector to facilitate the non-proliferation of weapons and weapons expertise.

The Partner has agreed to provide financial support for such project, under the DHHS Biotechnology Engagement Program (BTEP) and in accordance with the Article II, paragraph 2 of the Memorandum of Agreement.

As set forth in the ISTC Agreement, funds received by a legal entity in connection with the Center's projects shall be excluded in determining the profits of that organization for the purpose of tax liability and funds received by persons in connection with the Center's projects shall not be included in these persons' taxable incomes,

All parties to this Project Agreement shall conduct this project of work consistent with the principles of the ISTC Statute provisions and applicable international conventions and agreements for which the USA and Republic of Georgia are Parties.

HAVE AGREED AS FOLLOWS:

Article 1 - Scope of the Agreement

1.1 The Recipient shall carry out the work plan set forth in Annex I according to the conditions of the Agreement, subject to the provisions of the ISTC Agreement, the ISTC Protocol, the Statute of the Center (hereinafter referred to as "the ISTC Statute"), and the Principles for Partner Participation in ISTC Activities, which govern in case of conflict. The activities carried out under the Agreement are entitled: *Patterns of HIV drug resistance and molecular epidemiology of HIV in Georgia* – (hereinafter referred to as "the Project").

1.2 Subject to any special conditions in Article 11 or any amendments or exclusions by any other Articles, the detailed terms of the Agreement are specified in the Annexes that form an integral part of the Agreement. In the case of conflict between any provision in the Annexes and any other provision of the Agreement, the latter shall prevail.

1.3 The Partner may request through the Center access to the Project site for the consultation on and the evaluation of the progress of the Project. The Recipient shall use its best efforts to comply with such requests.

Article 2 - Duration of the Project

The duration of the Project is estimated to be 18 months from February 1, 2014 (hereinafter referred to as "the Operative Commencement Date").

Article 3 - Sub-agreements with Other Participating Institutions

The scope of work of each institution which takes part in the Project, the organizational structure of the Project, as well as financial requirements of such an institution, are defined and stipulated in Annex I. The Institute shall serve as the coordinating institution for all aspects of the Project, including the coordination of requests for payments for carrying out the work. In this regard, within 30 days after the Operative Commencement Date (or other appropriate time period mutually agreed upon), the Institute shall conclude sub-agreement with **Infectious Diseases, AIDS and Clinical Immunology Research Center** which cover all aspects of the involvement of these institutions in the Project and which clearly define the scope of work and responsibilities of each institution. These sub-agreements will provide an essential part of the legal, institutional, and financial framework for the execution of the Project. All rights and obligations of the Center and of the Institute as well as other conditions set forth in the Agreement shall be included in the sub-agreements. A copy of the sub-agreements shall be submitted to the Center without delay after the execution. The Institute and all participating institutions in such sub-agreements will hereinafter be referred to collectively as "the Recipient."

Article 4 - Financial Contribution of the Partner through the Center

4.1 The total cost of the Project to the Center shall not exceed US\$ 100,000.00 (One hundred thousand dollars and zero cents). This total includes:

- (1) items to be reimbursed in cash to the Recipient in accordance with Article 4.3,
- (2) grants in cash to be made by the Center directly to the individual participants in the Project (hereinafter referred to as "Individual Participants") for financial support of the Individual Participants in accordance with Article 4.4, and
- (3) items to be provided in-kind by the Center to the Recipient in accordance with Article 4.5.

After further consideration of the costs and availability of the items to be provided, the Recipient may, with the concurrence of the Center's representative, interchange items between Articles 4.3 and 4.5 with corresponding adjustments of the cost estimates for each Article.

4.2 The Partner shall provide to the Center project funds consistent with the bilateral financial Memorandum of Agreement between the Center and the Partner no later than the Operative Commencement Date of the Project.

4.3 The Center shall reimburse the Recipient for expenditures by the Recipient in accordance with Annexes I and II. The estimated cost of such expenditures is US\$2,948.

4.4 The Center shall make direct grants in dollars to Individual Participants in the Project in accordance with Annex I at an estimated cost of US\$50,452. This amount can be increased at the request of the Recipient and with the concurrence of the Center's representative and of the affected Individual Participants provided the costs of Article 4.3 and/or Article 4.5 are reduced accordingly.

4.5 The Center's in-kind contributions to the Recipient are estimated at US\$46,600. These in-kind contributions will be provided in accordance with the lists of items to be provided and the timetables set forth in Annex I in order to enable the Recipient to meet the work schedule for the Project. Failure by the Center to provide the in-kind contributions in a timely manner may give rise to a modification of the relevant provisions of the Agreement.

The Center's in-kind contributions, which are provided for exclusive use on the Project by the Recipient during the lifetime of the Project, include the following categories of items:

4.5.1 The Center shall provide in-kind equipment to the Recipient (if any) in accordance with Annex I (hereinafter referred to as "**Center Provided Equipment**"). Center Provided Equipment will be delivered to the Recipient at a CIS customs entry point specified by the Center. The Center will be responsible for clearance through customs, and the Recipient will be responsible for transporting the equipment from the customs entry point to the site of the Project. The equipment shall be inventoried, preserved, accounted for, and maintained throughout the Project by the Recipient. The equipment shall be used only in areas that are open for monitoring and auditing in accordance with Article 9. The title to Center Provided Equipment with an acquisition per item cost of less than \$2,500 will vest in the Recipient once it has been provided. The title to all other Partner Provided Equipment will remain with the Center, unless mutually agreed otherwise.

4.5.2 The Center shall provide in-kind materials in accordance with Annex I (hereinafter referred to as "**Center Provided Materials**"). Center Provided Materials will be delivered to the Recipient at a CIS customs entry point specified by the Center. The Center will be responsible for customs clearance, and the Recipient will be responsible for transporting the materials to the site of the Project.

4.5.3 The Center shall provide in-kind services (if any) in accordance with Annex I (hereinafter referred to as "**Center Provided Services**").

4.5.4 The Center shall provide in-kind international travel by the Recipient in accordance with Annex I (hereinafter referred to as "**Center Provided Travel**"). The cost of the Center's contribution will not exceed US\$10,140.

Center Provided Travel will be undertaken by participants in the Project only after advance approval for each trip by the Partner and notification to the Center. The Recipient shall send to the Partner and Center requests for travel not less than 30 days prior to the beginning of each trip unless a shorter time for advance request is approved by the Partner and then by the Center for a specific trip. The Center will provide directly to the traveler the funds to cover such travel, provided that such travel is approved by the Partner prior to the beginning of the travel.

The Center's responsibility does not include making arrangements for visits, passports, visas, or travel reservations but is limited to providing financial support, including funds to cover the costs of passport and visa fees as well as transportation and lodging, in accordance with the travel regulations of the Center.



The Recipient is responsible for ensuring that the financial support requested pursuant to this paragraph does not exceed the financial limit set forth above.

4.5.5 The Center shall provide in-kind the costs of certain bank transfer fees in accordance with Annex I (hereinafter referred to as "**Center Provided Bank Fees**"). They will be limited to fees necessary to transfer funds into the bank account or accounts of the Recipient and fees associated with the payment of cash to Individual Participants in the Project. They will be paid directly by the Center to the appropriate banks.

Article 5 - Cash Payments by the Center to the Recipient

5.1 Pursuant to Article 4.2, the Center shall make its payments to the Recipient through Dedicated Bank Account(s), as set forth in Article 6. 6 of Annex II in banks acceptable to the Center.

- An advance payment of US\$0 which is the estimated level of expenditures by the Recipient during the first six months of the Project, as soon as possible following the Operative Commencement Date;
- Quarterly payments within one month of the receipt by the Partner and Center of progress or annual reports and associated cost statements in accordance with Article 7 and Annexes II and III. The amounts of the payments shall be estimates by the Center of the funds required to support the work plan set forth in Annex I during each of the succeeding quarters taking into account the cost statement from the previous period;
- A retention shall be made by the Center of US\$2,948. The retention shall be released to the Recipient within one month following the approval by the Partner and Center of the last technical or financial document or other deliverable required by the Agreement.

5.2 Pursuant to Article 4.4, the Center shall make grant payments directly to Individual Participants in accordance with letters of agreement between the Center and the Individual Participants. The Center shall ensure that banking arrangements are established for these payments.

At the end of the third month following the Operative Commencement Date and every three months thereafter throughout the duration of the Project, the Recipient represented by the Project Manager who is identified in Annex I will provide the Partner and the Center with a list of grant payments that are due at that time to Individual Participants in accordance with the payment levels set forth in Annex I and the amount of time devoted to the Project by each Individual Participant as certified by the Project Manager. Such payments will then be promptly made as appropriate by the Center.

Since the Individual Participants will remain employees of the Recipient, the Center's act of direct grant payments to the Individual Participants will not transfer from the Recipient to the Partner or the Center any liability for damages caused by the Individual Participants during execution of the Projects or any liability for damages to the Individual Participants during execution of the Project.

Article 6 - Cost Statements by the Recipient

6.1 Quarterly cost statements shall be submitted by the Recipient to the Partner and the Center as follows:

To the Center, the Partner and the U.S. Counterpart Scientist:

- English: one copy via electronic transmission (e-mail or on diskette) and one printed copy;

The first statement is to be submitted no later than four months after the Operative Commencement Date and will cover the first three months of Project activity. Subsequent statements are to be submitted at three-month intervals following submission of the first statement. The statements will be appended to the relevant technical reports specified in Article 7. The cost statements will include the costs of grant payments directly to Individual Participants, but the requests for such grant payments in accordance with Article 5 should not be delayed pending preparation of the entire quarterly cost statements called for in this Article. Such payments may be nevertheless suspended by the Center in case if the cost statement for the previous quarter was not yet submitted to the Center.

6.2 A consolidated cost statement shall be submitted by the Recipient to the Partner and the Center within two months of the completion, cessation or termination of the work financed by the Partner as follows:

To the Center, the Partner and the U.S. Counterpart Scientist:

- English: one copy via electronic transmission (e-mail or on diskette) and one printed copy;

If such a statement is not submitted on time, the Center or the Partner may request in writing its submission. If the Center and the Partner do not receive the submission within thirty days after such a written request, the Center, in consultation with the Partner, may consider the previously claimed costs to be final and determine to make no further reimbursement.

6.3 Cost statements shall comply with the formats prescribed in Annex III.

Article 7 - Reports and Other Project Outputs

7.1 The Recipient shall submit the following reports in accordance with the format prescribed in Annex III as follows:

To the Center, the Partner and the U.S. Counterpart Scientist:

– English: one copy via electronic transmission (e-mail or on diskette) and one printed copy;

It is the responsibility of the Recipient, in consultation with the Partner, to indicate clearly what parts of reports and other project outputs contain invention or business confidential information and specify any limitations on circulation. For each report or other project output, an unrestricted version shall also be provided. All reports containing invention or business confidential information shall be handled by the Center according to established internal procedures.

- Quarterly progress reports covering each three-month period following the Operative Commencement Date to be submitted within one month after the end of each reporting period.
- Annual reports. For projects of duration of more than one year, an annual report will be submitted 13 months after the Operative Commencement Date and will cover the first year of project activity. For projects of duration of more than two years, a second annual report will be submitted 12 months later.
- Other reports. The Recipient and the Partner will define other reports in Annex I.
- A final report. A draft final report will be submitted to the Center and the Partner within two months of the completion of the Project work plan, cessation or termination of the Agreement, or the agreed completion date of the Agreement, whichever is the earliest. The Partner, in consultation with the Center, shall submit to the Center and Recipient its evaluation and comments on the draft final report within two months after receipt of the latter. The definitive final report will then be submitted by the Recipient to the Center and the Partner within one month after receipt of the Partner's evaluation. If the Partner does not submit an evaluation within two month, the draft final report shall be considered the definitive final report.
- Edited reports for publication will be provided as specified in Article 4.1 (c) of ANNEX II.

7.2 For the purposes of the Agreement, "deliverables" are defined as any significant outputs, including all reports, of the Project to be submitted in accordance with Annexes I, II and III.

Article 8 - Ownership and Exploitation of Results

8.1 The results arising from the Agreement shall be allocated between the Recipient and the Partner in accordance with Part E of Annex II. The Recipient and the Partner shall take appropriate action to exploit or commercialize the results and to make available the results to third parties in accordance with the framework specified in Part E of Annex II. Cooperation agreements with foreign institutions complementing, but not conflicting with, this Framework may be entered into by the Recipient and the Partner.

8.2 Prior to completion of the Project, the Recipient shall submit to the Center a Technology Implementation Plan developed in consultation with the Partner. For projects with a duration of eighteen months or longer, this Plan will be submitted 6 months prior to the anticipated Project completion date. For projects with a duration of less than eighteen months, the Plan will be submitted three months prior to the anticipated Project completion date.

8.3 Exploitation of results shall be limited to applications for peaceful purposes. In this regard, the Recipient and the Partner shall ensure that any results which could result in concerns over proliferation of weapons technology and transfer of sensitive technologies will be protected in accordance with relevant laws of the Republic of Georgia and international agreements and conventions to which the Republic of Georgia is a Party.

Article 9 - Auditing and Monitoring

9.1 Access by the Center to carry out on-site monitoring of all technical activities of the Project shall be granted by the Recipient, and information and assistance shall be given for the verification and evaluation of the Project activities as set out in Annex II.

9.2 Financial audits of costs may be carried out by the Center as specified in Annex II.

9.3 Auditing and Monitoring of institutions located in closed cities shall be carried out according to the procedures adopted at the sixth Governing Board Meeting of the Center.

Article 10 - Amendments, Variations, or Additions

The provisions of this Agreement and its Annexes may be amended or supplemented only by means of a written agreement signed by authorized representatives of the Signatory Parties. However, operational changes in Annex I, other than changes in the Project Manager, the Participating Institution, daily rates of leading persons of the Project and the overall schedule, can be made by agreement between the Center and the Recipient.

Article 11 - Special Conditions

11.1 With respect to the Protection of Human Subjects

- (i) The NIH/NIAID has reviewed the proposed activities and found that they do consist of research involving human subjects.
- (ii) The project proposal must be reviewed in accordance with the U.S. law and international policies and regulations regarding biomedical research involving human subjects
- (iii) The Implementing Agencies shall be responsible for ensuring that any research work conducted under this project Agreement shall be carried out consistent with The Public Health Service Act as Amended by the Health Research Extension Act of 1985 and the Federal Policy for the Protection of Human Subjects of 1991
- (iv) The Recipient and the Partner shall follow the principles of *The Belmont Report, Principles and Guidelines for Protection of Human Subjects of Research* or *The World Medical Association Declaration of Helsinki, Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects*, adopted by the 18th World Medical Assembly and revised in 1989.

11.2 With respect to the use of Laboratory Animals

- (i) Laboratory animals and/or endangered species are not expected to be a subject of this research or be involved during the execution of work under this specific project.
- (ii) However, if this proves otherwise, the project proposal must be reviewed in accordance with the U.S. law and international policies and regulations regarding biomedical research involving laboratory animals
- (iii) The Implementing Agencies shall be responsible for ensuring that any activity carried out pursuant to this agreement and involving laboratory animals is in compliance with the Foreign State of Compliance, International Guiding Principles for Biomedical Research and the Public Health Service Policy on Humane Care and Use of Laboratory Animals as revised in September of 1986

11.3 With respect to transport of Biological Samples

Any export/import involving transportation of biological samples shall be conducted in accordance with the existing laws, regulations, and administrative procedures of the United States of America and the Republic of Georgia. For current information regarding this issue please contact the following:

- (i) For U.S. exports: Department of Commerce, Bureau of Export Administration at (202) 482-4811.
- (ii) For U.S. imports of etiologic agents of humans: Centers for Disease Control and Prevention, Office of Health and Safety at (404) 639-2453.
- (iii) For U.S. imports of etiologic agents of livestock, poultry and other animals: United States Department of Agriculture, Animal and Plant Health Inspection Service, Veterinary Services at (301) 734-3277.

11.4 With respect to Manipulation of Genetic Material through the Use of Recombinant DNA Techniques

- (i) The CDC has reviewed the proposed activities and found that they do not consist of research involving recombinant DNA techniques for genetic manipulation.
- (ii) However, if this proves otherwise, the project proposal must be reviewed in accordance with applicable U.S. law and international policies and regulations, including the current "NIH Guidelines for Research Involving Recombinant DNA Molecules." These guidelines can be found on the NIH website at <http://www.nih.gov/od/oba> or from the NIH Office of Recombinant DNA Activities (301-496-9838).
- (iii) The BTEP Advisory Group may ask the investigators to initiate a review by the appropriate Recombinant DNA Advisory Committee (RAC) or Institutional Biosafety Committee (IBC) at any time.

Article 12 - Disputes

Disputes arising during performance of this Agreement including, in particular:

- (i) A claim by the Recipient for any payments deemed due;
- (ii) An interpretation of a provision of the Agreement; or
- (iii) A request for relief or approval related to the Agreement,

shall be subject to the following procedure:

The Recipient shall submit any claim, demand, or request in writing to the Partner and to the Center. The Partner and the Center will prepare a joint response. Unless a longer period is specified in the Agreement, the written decision of the Partner and the Center shall be delivered to the Recipient within four weeks of the receipt of the submission.

Exceptionally, the Recipient may appeal the Partner's and Center's decision in writing through the Executive Director of the Center to the Governing Board of the Center within four weeks of the communication of the Partner's and Center's decision.

The decision of the Governing Board shall be final and binding (unless otherwise provided). Pending the final settlement of disputes, the Recipient shall, nevertheless, proceed diligently with the performance of the Agreement.

Article 13 - Liability

13.1 The Partner and the Center shall not be liable for any material loss, damage, or injury of any nature arising from, or in connection with, the performance of the work under the Agreement solely by virtue of financing the Project, including liability from direct grant payments to Individual Participants as set forth in Article 5.2.

13.2 The Partner and the Center shall not be liable to the Recipient or third parties for claims arising from:

- publication or transmission of any report in accordance with Articles 4 and 13 of Annex II unless it is shown that the Partner or Center have not taken reasonable steps to protect material clearly indicated as invention or business confidential information;
- the application of the contents of any report by a third party; or
- the handling or use of products which result from the Project.

13.3 The Center shall not be liable for nonperformance by the Partner or the Recipient of their obligations under the Agreement.

Article 14 - Suspension and Termination of the Agreement

14.1 Suspension

14.1.1 If the Center identifies a problem with the Project's performance through audit, monitoring, annual reports or other ways, and discussions between the Center and the Recipient which shall ensue pursuant to a notice given by the Center to the Recipient do not produce any results, the Center shall reserve the right to suspend, in consultation with the Partner, the project or, when feasible from technical and other points of view, a part of the Project, within thirty days after the Center issues to the Project Manager a notification of suspension which specifies the problem, the effective date and the period of the suspension. In case auditing and monitoring procedures stipulated in the Agreement and Annex II are breached by the Recipient, the suspension shall come into force ten days after the notification given to the Recipient if no corrective action has been taken during this period.

When the suspension becomes effective, the Center shall pay grants to the individual participants for the period they were engaged in the Project before the Center's declaration of suspension becomes effective. Any other payments or in-kind supplies to the Recipient shall in principle be suspended as long as the suspension remains in effect. The Recipient shall act in due diligence to mitigate any losses which may arise during this period.

Even when the suspension is in effect, the Center and the Recipient shall do the utmost to find a possible solution to the problem.

14.1.2 In case the Center and/or the Partner does not fulfill its obligations arising from the Project, namely in relation to Article 2 and 3, the Recipient shall reserve the right to suspend the Project within thirty days after the Recipient issues to the Executive Director of the Center a notification of suspension which specifies the problem, the effective date and the period of the suspension. Clauses of paragraph three of 14.1.1 shall be applied here as well.

14.2 Termination

14.2.1 When the Project is suspended by the Center, and the period of the suspension which is specified in the Center's notification expires and the Center and the Recipient are unable to find a solution, the Center shall, in consultation with the Partner, terminate the Project. In the event of partial suspension, the Center and the Recipient shall negotiate and agree upon possible measures including partial termination of the Project. If these negotiations do not produce any viable alternative plan, the Center shall reserve the right to terminate the entire Project.

Notwithstanding the termination, the Recipient shall submit reports and cost statements covering the period up to the termination and the following provisions of the Agreement shall continue to apply: Article 12 (Disputes), Paragraph 7 (Accounting Principles, Allowable Costs, and Transfer of Costs) and 8.2 (Equipment) of Annex I of the Agreement, and Part E of Annex II of the Agreement (Information and Intellectual Property).

If the Project is terminated, costs shall be limited to the allowable costs incurred by the Recipient prior to the suspension and other costs which the Center considers to be fair and reasonable having regard to commitments which have been reasonably entered into and which cannot be canceled or avoided.

14.2.2 When the Project is suspended by the Recipient, and the period of the suspension which is specified in the Recipient's notification expires and the Recipient and the Center are unable to find a solution, the Recipient shall terminate the Project. Clauses of paragraphs two and three of 14.2.1 shall be applied here as well.

14.3 Termination by Force Majeure Situations

When Force Majeure situations occur which make the Project implementation impossible, the Center in consultation with the Partner and the Recipient may terminate the Project with application of similar procedures as specified above.

14.4 Termination Forced due to the Violation of Laws or Regulations by the Recipient

When the Recipient has committed actions which obviously violate the national laws of the state where the Recipient is a legal entity or which obviously are contrary to the stated objectives of the Center or to other conditions specified under the ISTC Agreement or the ISTC Statute, the Center shall terminate the Project with immediate effectiveness upon written notification of termination to the Recipient. In this case, the Recipient shall promptly return to the Center all payments and goods previously provided to the Recipient. Notwithstanding any termination, Part E of Annex II of the Agreement will continue to apply.

Article 15 - Correspondence

15.1 Any written notice, request or consent required under the Agreement is deemed to have been given or made when delivered in person to an authorized representative of a Signatory Party or when sent by mail, telex, telegram, electronic mail or facsimile (receipt acknowledgment required) to such Signatory Party at the following address:

For the Center:
International Science and Technology Center
32-34 Krasnoproletarskaya Str.,
Moscow 127473, Russia
Facsimile: +7(499)978-4926
Senior Project Manager: Patrick Russo

For the Recipient:
National Center for Disease Control and Public Health of Georgia
9 Asatiani Str, Tbilisi, 0177, Georgia
Facsimile: +995 32 231 17 55
Project Manager: Irma Burjanadze

For the Partner
National Institutes of Health National Institute of Allergy and Infectious Diseases
6610 Rockledge Drive, Ste 2500
Bethesda, MD, 20892, USA
Facsimile: +(310) 402-3255
NIH/BTEP Program Manager: William Rosa

For the U.S. Counterpart Scientist:
Emory University
1518 Clifton Road,
Atlanta, GA 30322, USA
Tel.: +1(404) 639 5310
Chair of Hubert Department of Global Health: Carlos del Rio

15.2 Notice will be deemed to be effective as follows:

- (i) in the case of personal delivery or mail, on delivery;
- (ii) in the case of telexes, telegrams, electronic mail or facsimiles, within one (1) working day following confirmed transmission. A signed original will be provided by mail in all cases.

15.3 Each Signatory Party may change its address for notice hereunder by giving the other Party notice of such change pursuant to this Article.

Article 16 - Annexes

As specified in Article 1.2, the Annexes are an integral part of the Agreement. They are:

Annex I	Work Plan
Annex II	General Conditions
Annex III	Formats for Progress and Cost Reports
Annex IV	Disclaimer

Article 17 - Entry into Force of the Agreement

The Agreement shall enter into force on February 1, 2014.

Prepared in Moscow in the English language.

For the Center

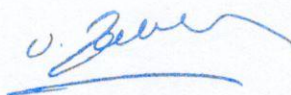


David Cleave
Acting Executive Director
ISTC

11 Feb 2014

(date)

For the Recipient



Amiran Gamkrelidze
General Director
National Center for Disease Control
and Public Health

19 Feb. 2014

(date)

For the Partner

William Rosa
NIH/BTEP Program Manager
NIH/NIAID

(date)

ANNEX I
Work Plan
I. Summary Project Information

1. Project Title

Patterns of HIV drug resistance and molecular epidemiology of HIV in Georgia

2. Project Manager

Name: Irma Burjanadze	
Title MD :	Position Coordinator of National Program on HIV/AIDS (Epidemiologist)
Street address: 9, M. Asatiani St.	
City: Tbilisi	Region:
ZIP: 0186	Country: Georgia
Tel.: +995 595 95 61 21	Fax: +995 32 231 17 55
E-mail: irmaepi@gmail.com; i.burjanadze@ncdc.ge	

3. Participating Institutions

3.1. Leading Institution

Short reference: NCDC	
Full name: National Center for Disease Control and Public health	
Street address: 9, M. Asatiani St.	
City: Tbilisi	Region:
ZIP: 0186	Country: Georgia
Name of Authority: Signature Amiran Gamkrelidze	
Title MD, PhD :	Position Director General :
Tel.: +995 32 231 17 55	Fax: +995 32 231 17 55
E-mail: a.gamkrelidze@ncdc.ge	
Governmental Agency: Ministry of Health, labor and Social Affairs of Georgia	

3.2. Other Participating Institutions

Participant Institution 1

Short reference: National AIDS Center	
Full name: Infectious Diseases, AIDS and Clinical Immunology Research Center	
Street address: 16 Al. Kazbegi Avenue	
City: Tbilisi	Region:
ZIP: 0160	Country: Georgia
Name of Signature: Shota Gogichaishvili	
Authority:	
Title: MD, PhD	Position: Executive Director
:	:
Tel.: (995 32) 2395659	Fax: (995 32) 2399144
E-mail: aids@gol.ge	
Governmental Agency: Ministry of Labour, Health and Social Affairs of Georgia	
Sub-manager: Nikoloz Chkhartishvili	
Title: MD, MS	Position: Head of Research Team
:	:
Tel.: (995 32) 2398018	Fax: (995 32) 2399144
E-mail: nikoloch@yahoo.com	

4. Foreign Collaborators/Partners

4.1. Collaborators

Institution: Emory University	
Street address: 1518 Clifton Road	
City: Atlanta	Region/State: GA
ZIP: 30322	Country: USA
Person: Carlos del Rio	
Title: MD	Position: Chair of Hubert Department of Global Health
:	:
Tel.: 404-727-8797	Fax: 404-727-4590
E-mail: cdelrio@emory.edu	

Institution Johns Hopkins University	
:	
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4.2. Partners

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5. Project Duration

18 months

6. Project Location and Equipment

Institution	Location, Facilities and Equipment
Leading Institution	Facilities of the National Center for Disease Control and Public Health (NCDC) include main building located at 9 M Asatiani str. Tbilisi, 0186, Georgia and Richard G. Lugar center for Public Health Research (CPHR) located at 16, Kakheti highway. Tbilisi, 0109, Georgia The following spaces will be utilized for project implementation NCDC main building: Office #301, #207; #513 Block I, #202, Training center; CPHR: #1150B, Richard G. Lugar Center laboratory The NCDC is the premier research and public health service center in Georgia and staffed with experienced clinical microbiologists, epidemiologists, research scientists, veterinarians and public health service administrators. The NCDC serves as the Central State Laboratory for Georgia. The Molecular Epidemiology and Microbiology Laboratory maintains several rooms including a pre-PCR and a post-PCR rooms.

	The following equipments are available: Biological Safety Cabinet, Class II, type 2A/B3; Thermocyclers, Techne - 3 units; Horizontal and vertical electrophoresis equipment, BioRad, Serva; PFGE BioRad CHEF-DR-II System; Blotting and Hybridization Equipment; Genetic Analysis System CEQ-8000 Beckman Coulter, Sequencer - ABI 3130XL; WGS - Illumina MiSeq platform; Ultracentrifuge, Sorval, 4 centrifuges for 1.5ml eppendorf tubes, 14000rpm, two -200 C freezers; PCR Workstations; Water Baths; Autoclave; Thermostats;
Participant Institution 1	Infectious Diseases, AIDS and Clinical Immunology Research Center (National AIDS Center) is the country's reference institution for HIV diagnosis, treatment and care. The Center is acclaimed internationally for excellence in clinical care, biomedical research and medical education. National AIDS Center has the following departments and divisions: Clinical department, Laboratory service, Research department, Epidemiological division and IT department. Clinical department includes: emergency/admissions block, an in-patient unit that accomdates 172 beds, diagnostic unit and out-patient clinics for HIV/AIDS, viral hepatitis, GI infections, and other infectious disease. Epidemiological division operates HIV testing and counseling (HTC) unit, which is the single largest provider of HTC services in the country. The Center provides care to approximately 70% of registered HIV patinets. The laboratory service consists of six laboratories: 1) Laboratory of Clinical Diagnostics and Clinical Chemistry; 2) Laboratory of HIV Diagnostics; 3) Laboratory of Clinical Virology; 4) Laboratory of Clinical Immunology; 5) Laboratory of Molecular Medicine and 6) Laboratory of Bacteriology. Laboratories are designed to comply with biosafety level 2 standards. There is well-developed infrastructure for practical applications and scientific research. Laboratory service of the National AIDS Center successfully participates in WHO-recognized annual quality assurance program of the Australian National Serology Reference Laboratory. Proposed laboratory methods will be performed at the Laboratory of Molecular Medicine, which relevant technical and human capacity. The following equipment is available at the laboratory to conducting proposed investigations: Genetic Analyzer 3500XL (Applied Biosystems, USA) - 1; GeneAmp PCR System 9700 (Applied Biosystems, USA) - 2; 7500 Real Time PCR System (Applied Biosystems, USA) - 1; COBAS TAQMAN 48 Real Time PCR system (Roche, Germany) - 1; Biosafety Cabinet BSL II (Fisher Scientific, USA; Labconco, USA) - 3; Ultra low freezers (NuAire, USA; Sanyo, Japan) - 2; Refrigerated centrifuge micro-22R (Hettich, Germany); DB-20 Dry-Block (Techne, Germany) - 1; Microwave oven (Panasonic, Japan) -1; Water bath ST402 (NUVE, Turkey) - 1; Vortex Mixer IKA-VibroFix VF2 (Labortechnik, Germany); Horizomtal Mini Gel, Model B2 (Owl Scientific, USA) - 1. National AIDS Center is equipped with more than 100 personal computers. Computers are connected to network and have access to internet and email for rapid communication.

II. Specific information

1. Introduction and Overview

HIV/AIDS remains one of most serious global health challenges. Since the first cases of AIDS reported in 1981, HIV/AIDS evolved to pandemic level composed of multiple epidemics at regional and national levels.[1] Globally, 34 million people are living with HIV, including 1.4 million individuals in the countries of former Soviet Union (FSU). Although global solidarity in AIDS response has brought substantial health gains, HIV continues to exact substantial toll with 1.7 million lives lost to the disease in 2011 only.[1]

Advent of combination antiretroviral therapy (ART) in mid 1990s dramatically changed the course of the epidemic. ART significantly improves health and life-expectancy of people living with HIV.[2, 3] Until recently ART was widely available only in developed countries. The momentum generated by the World Health Organization's (WHO) "3 by 5" strategy[4] resulted in massive expansion of access to ART in resource limited settings. According to WHO, 9.7 million people were receiving life-saving treatment in low- and middle-income countries by the end of 2012, representing dramatic 25-fold increase compared to 2003.[5] More recently it has become clear that ART not only saves lives but also prevents new HIV infections.[6, 7] The ability of ART to significantly reduce the risk of HIV transmission led to the concept of treatment as prevention, which currently is embraced as critical component of combination HIV prevention.[8]

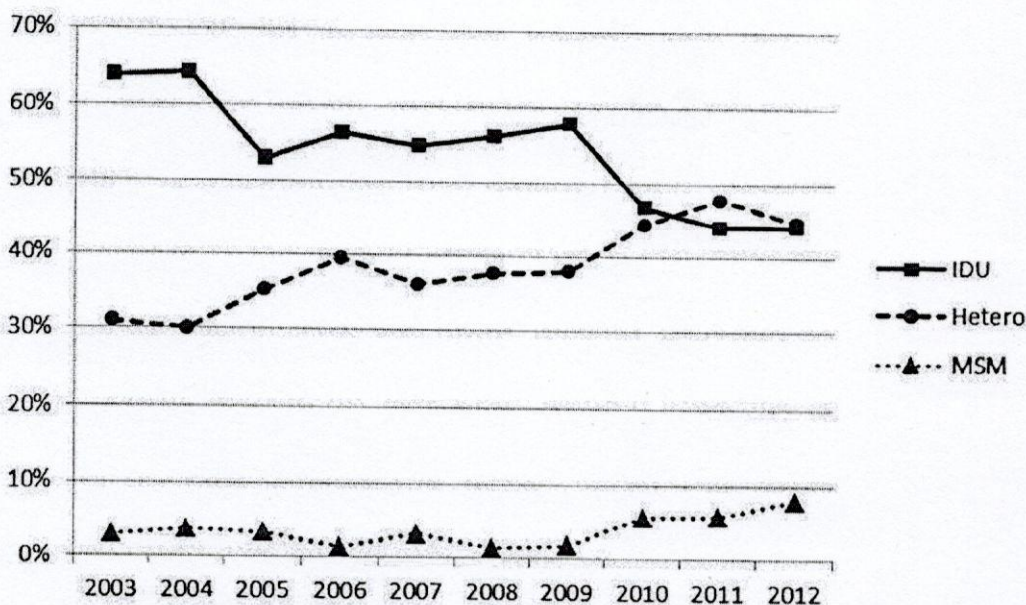
However, along with the obvious benefits in terms of reducing HIV-related morbidity and mortality, as well as HIV incidence, there are concerns related to increasing use of antiretroviral drugs (ARVs). The potential for widespread emergence and transmission of HIV drug resistance to ARVs has been a major public health concern. Transmitted drug resistance (TDR), i.e. acquiring drug-resistant HIV, has been first described in early 1990s.[9] In resource-rich countries, where ART has been available since its introduction, TDR account for 10-20% of new infections.[10-12] Recent meta-regression analysis showed that rapid roll-out of ART in low- and middle-income countries resulted in increase in TDR. The rates ranged from 4 to 8%, representing estimated increase of up to 29% per year since 2003.[13] To respond to the growing threat of resistant HIV epidemic, it is now recommended to implement HIV drug resistance surveillance to inform HIV-related health programs.

In addition to HIV drug resistance, monitoring of molecular epidemiology of HIV provides important evidence both for clinical and public health decision-making. Because of error-prone nature of replication and high mutation and recombination rates HIV is characterized by high genetic variability.[14-16] HIV-1 group M, responsibly for vast majority of HIV cases globally, is categorized into 9 main subtypes (A-D, F-H, J, and K), and 48 circulating recombinant forms (CRF).[16]

HIV genetic diversity can affect disease progression, response to ART and emergence of drug resistance, and even transmission efficiency. [17-20] The HIV influence on susceptibility to individual antiretroviral drugs and the tendency of HIV to select certain resistance mutations is of particular importance in resource limited settings. Resistance pathways in different subtypes may affect drug cross-resistance and the potential use of specific second-line regimens, which further narrows limited treatment options in developing countries.[21, 22] Phylogenetic analysis of HIV sequences has been recognized as important tool for assessing the dynamics of the epidemic. This is the molecular epidemiological strategy that characterizes HIV epidemic by assessing genetic relatedness between viral sequences. Combined with epidemiological, demographic and behavioral data, phylogenetic analysis insights into the underlying structure of transmission networks, also referred to as transmission clusters. Introduction of drug resistance programs in early 2000s in resource-rich settings provided large sequence datasets of *pol* gene of HIV that helped to better understand transmission trends of local and regional epidemics.[23-28]

The first case of HIV infection in Georgia was reported in 1989. At the end of 2012, a cumulative 3,641 cases of HIV infection were registered in the country. The annual number of reported HIV cases has risen each year. Over the last decade the rates of new diagnosis in Georgia more than quadrupled from 2.2 to 10.1 cases per 100,000 population. Similar to other FSU countries, the epidemic in Georgia has been primarily driven by injection drug use (IDU) accounting to 54% of total reported cases. However, recent trends indicate significant increase in the proportion of heterosexually acquired infections (figure 1). Surveillance data suggests that this increase is largely due to HIV positive IDUs transmitting the virus to their female sexual partners.[29]

Figure 1. Distribution of newly reported cases by transmission category (2003-2012)



The epidemic is also on the rise among men who have sex with men (MSM). Annual trends in new HIV diagnosis indicate more than 2-fold increase in the proportion of homosexually acquired infections compared to 2003. Nevertheless, in terms of absolute number MSM account only 4% of total reported cases. In addition to routine surveillance data, studies indicate potential for the surge of the epidemic among MSM. The HIV prevalence in this population increased from 4% in 2007 to 13% in 2012.[30] In another study, history of male-to-male sex was significantly associated with probability of having recent infection.[31]

The spread of the virus in Georgia had been closely linked to the evolution of HIV epidemic in Eastern European region. Georgia's HIV epidemic is dominated by subtype A1 virus found in other FSU countries.[32, 33] During the early stages of the epidemic, majority of reported cases were among temporary labor migrants returning from Russia and Ukraine. This helps to explain the high genetic similarity between viral isolates from Georgia and other countries of the region.[34, 35]

The last surveys of TDR conducted in Georgia in 2006-2008 showed low level of primary drug resistance (2.4%). It should be taken into consideration that Georgia that antiretroviral drugs in Georgia have been widely available just before the survey was conducted. Since 2004, Georgia remains the only FSU country to achieve universal access to ART.[36] At the end of 2012 1640 persons living with HIV were receiving ART, representing more than 30-fold increase compared to 2004. As recent meta-regression analysis showed that changes in TDR can be observed after at least 5 years since the roll-out of ART.[13] Therefore it is valid to assume that 10 years of universal ART may have increased vulnerability to the risk of TDR.

Dynamics of HIV epidemic in Georgia (shift to heterosexual transmission and surge of the epidemic in MSM) along with increasing number of patients receiving ART, justify the need of conducting the proposed study. The goal of this study is to expand knowledge on HIV drug resistance and better understand driving forces of the epidemic in Georgia. The long-term objective is to move obtained knowledge into effective treatment and prevention strategies. Specific aims of the study include:

Specific aim 1: Analyze patterns of HIV drug resistance

- Estimate the prevalence of transmitted drug resistance (TDR) among newly diagnosed HIV patients
- Characterize drug resistance profile among ART-experienced patients

Specific aim 2: Evaluate time trends in molecular epidemiology of HIV

- Characterize distribution of HIV subtypes among newly diagnosed HIV patients enrolled in the study
- Evaluate time trends in subtype distribution
- Analyze transmission clusters

Specific aim 3: Establish national HIV sequence database

Study will use hybrid design combining prospective and retrospective data to accomplish proposed aims. For the prospective component the study will enroll 150 patients newly diagnosed with HIV. Retrospective component will use secondary data, including HIV sequences and patient-related information, from 234 ART-



naïve HIV patients diagnosed during the period of 1998-2012 and from 250 ART-experienced patients failing on therapy.

TDR will be estimated in 150 ART-naïve HIV patients diagnosed with HIV within the 3 months prior to date of enrollment. Taking into account small share of MSM among people living with HIV in Georgia and a growing epidemic in this population, the study will oversample MSM to achieve the sufficient representativeness of the population. This will also allow us to better characterize transmission patterns in phylogenetic analysis. HIV genotypic resistance testing will be performed using ViroSeq™ HIV-1 Genotyping System (Abbott diagnostics, Wiesbaden, Germany) on 24 capillary automated 3500x1 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). Prevalence of transmitted drug resistance will be estimated using the WHO surveillance drug-resistance mutations list.[37]

Drug resistance profiles among ART-experienced patients will be characterized using secondary data available at National AIDS Center. HIV drug resistance test is performed routinely among patients failing on therapy and all such patients will be included in the analysis. We expect that data from at least 250 patients will be available at the time of study inception. Previous description of patterns of HIV drug resistance among treatment-experienced patients suggested that HIV subtype A1 has distinct resistance profile.[36] However, the generalizability of this finding was limited because of small sample size (65 patients). Larger sample size of the proposed research will provide proof whether viral strains circulating in Georgia truly have differential patterns of resistance-conferring mutations.

Trends in molecular epidemiology will be evaluated in phylogenetic analysis. Viral sequences from 150 newly enrolled patients and 234 ART-naïve patients from previous studies will be used for this purpose. The consensus nucleotide sequences consisting of entire HIV-1 protease gene from codons 1 to 99 and two-thirds of the reverse transcriptase (RT) gene from codons 1 to 335 will be used for reconstructing phylogenetic trees and identification of transmission clusters. The analysis will integrate molecular, demographic and epidemiological data to describe structure of transmission clusters. Previous research showed close genetic linkage between IDU and heterosexual epidemics in Georgia.[35] Unfortunately, MSM were poorly represented in this study and it was impossible to make meaningful conclusion whether MSM epidemic develops independently or not. Oversampling of MSM in the proposed study will allow us to study transmission events within the population and assess linkages with IDU-driven epidemic.

The implementation of the proposed study will enable us to establish national HIV sequence database. The database will be designed to serve as systemized repository of viral sequences and drug resistance tests performed as part of routine clinical care and research among treatment-naïve and treatment-experienced patients. Important features of the database will be its integration with national HIV/AIDS clinical database, which contains information on every known case of HIV infection diagnosed in Georgia since the start of the epidemic. This will provide patient-level linkage of sequencing data to patient characteristics, including demographic, epidemiological, clinical and laboratory data.

Currently, National AIDS Center stores HIV sequences in FASTA format as standalone files. Stored sequences are not directly linked to either drug resistance reports or patient-level data, and require additional efforts to gather this information. Establishing sequence database will help to overcome this shortcoming, which provides opportunity to perform comprehensive analysis on the epidemiology and clinical aspects of HIV drug resistance and genetic diversity.

The proposed study will be implemented by the National Center for Diseases Control and Public Health (NCDC, leading institution) in collaboration with the Infectious Diseases, AIDS and Clinical Immunology Research Center (National AIDS Center, participating institution). While, NCDC is the country's key national agency responsible for coordinating HIV/AIDS surveillance and national HIV Monitoring and Evaluation system, the National AIDS Center is the country's referral institution for HIV diagnosis, treatment and care. Taking into account their mandate the two institutions have established close cooperation within the framework of national HIV response. NCDC and National AIDS Center have experience of successful research collaboration in various areas of infectious diseases. One of the best examples of this collaboration is the ISTC supported study of "Epidemiology, Molecular Characteristics and Clinical Course of HCV Infection in Georgia" (#G-616).

As the leading institution NCDC will take overall responsibility for project management. Dr. Irma Burjanadze (NCDC) will be designated as project manager and Dr. Nikoloz Chkhartishvili (National AIDS Center) will be designated as sub-manager to coordinate activities at the supporting institution. Dr. Tengiz Tsertsvadze (National AIDS Center) will provide scientific guidance on project implementation in his capacity of scientific leader. Given the existing technical infrastructure, experience and expertise needed for HIV genotyping/resistance testing, all proposed laboratory methods will be performed at the laboratory of molecular

medicine of the National AIDS Center. Laboratory group will include scientists from NCDC and National AIDS Center. NCDC will also contribute to data acquisition and management, and analysis, and clinical group of the National AIDS Center will be responsible for selection and recruitment of study subjects.

2. Expected Results and Their Application

The study is anticipated to generate valuable knowledge to guide design of effective prevention and treatment interventions.

- Prevalence of TDR after 10 years of universal ART will be determined and temporal trends will be assessed.
- Drug resistance pathways characteristic to HIV strains circulating in Georgia will be described.
- Trends in HIV subtype distribution will be determined.
- Thorough knowledge on structure of local transmission clusters will be obtained by integrating molecular, demographic, epidemiological and spatial data.
- National HIV sequence database will be established.

Detailed characterization of patterns of HIV drug resistance among ART-naïve and ART-experienced patients will be essential for informing national treatment guidelines, in terms of selection first- and second-line regimens, and the routine use of baseline HIV drug resistance testing. In addition, assessment of temporal trends in TDR can serve as key indicator of performance of ART program.

Molecular studies can provide important dimension in HIV surveillance by identifying geographic, demographic or epidemiological "hotspots" fueling HIV transmission in the country, thus providing basis for tailoring response to the need.

Finally, creation of centralized repository of HIV sequences with linkages to HIV drug resistance and other patient-level data allows to establish comprehensive monitoring of drug resistance and molecular epidemiology. This will provide important insights into the epidemiology and clinical aspects of HIV drug resistance, as well as into the transmission dynamics.

3. Meeting ISTC Goals and Objectives

Implementation of the proposed study will allow weapon scientists and other high skilled specialists to direct their knowledge and skills towards complex scientific and public health problem of HIV. Weapon scientists from NCDC and National AIDS Center, to be involved in the project implementation, have extensive experience of working on especially dangerous pathogens. Many of them are currently classified by National Institute of Allergy and Infectious Diseases as biodefense category A and B microorganisms. Overall, it is planned to involve 7 weapon scientists from both institutions, representing 54% of total project personnel.

The proposed study will stimulate effective collaboration between Georgian and US institutions and scientists. This collaboration will support transfer of knowledge and strengthening biomedical research capacity in Georgia.

Findings of the study will be widely disseminated through publication in international peer-reviewed journals and presentation at international conferences, thus contributing to integration of Georgian researchers into international science community.

4. Scope of Activities

Task 1

Task description and main milestones		Participating Institutions
1. Patient selection and recruitment	2. Collection of specimens and research data	1-NCDC
		2-National AIDS Center
Description of deliverables		
1	150 newly diagnosed HIV patients are recruited by the Quarter 5	



Task 2

Task description and main milestones		Participating Institutions
1. HIV genotypic drug resistance testing		1-NCDC 2-National AIDS Center
2. Estimation of transmitted drug resistance		
Description of deliverables		
1	Abstract for international meeting is prepared	
2	Manuscript for international peer-reviewed journal is prepared	

Task 3

Task 3

Task description and main milestones		Participating Institutions
1. Extraction of data on patients failing on ART		1-NCDC 2-National AIDS Center
2. Analysis of HIV drug resistance profile		
Description of deliverables		
1	Abstract for international meeting is prepared	
2	Manuscript for international peer-reviewed journal is prepared	

Task 4

Task 4

Task description and main milestones		Participating Institutions
1. Subtype determination and phylogenetic analysis		1-NCDC 2-National AIDS Center
2. Characterization of transmission clusters		
Description of deliverables		
1	Abstract for international meeting is prepared	
2	Manuscript for international peer-reviewed journal is prepared	

Task 5

Task description and main milestones		Participating Institutions
1. Establish national HIV sequence database		1-NCDC 2-National AIDS Center
Description of deliverables		
1	Database protocol is developed and procedures tested	
2	All available HIV sequence and related data are entered into databases by the end of the project	

5. Role of Foreign Collaborators/Partners

The proposed project will be implemented in collaboration with well-acknowledged U.S. scientists Dr. Kenrad Nelson, Johns Hopkins University, and Dr. Carlos del Rio, Georgian and U.S. scientists will have intensive telephone and internet-based communication to ensure provision of technical assistance and consultation on the effective implementation of the proposed activities. U.S. collaborators will review technical reports and assist in preparation of scientific reports, such as abstracts, presentations and manuscripts. Study will also support training of Georgian scientists at U.S. collaborating institutions.

The proposed study will contribute to further expanding existing collaborations with Johns Hopkins and Emory University. Dr. Nelson substantially contributed to the first evaluation of HIV drug resistance and genetic diversity in Georgia. This work resulted in highly cited article, which significantly added to the limited information on the development of HIV epidemic in the Eastern European region (Zarandia M, Tsertsvadze T, Carr JK, Nadai Y, Sanchez JL, Nelson K. HIV-1 genetic diversity and genotypic drug susceptibility in the Republic of Georgia. *AIDS Res Hum Retroviruses* 2006;22:470-476).

6. Technical Approach and Methodology

Study design and population

Study will use hybrid design combining prospective and retrospective data to accomplish proposed aims. We will prospectively enroll 150 HIV patients newly diagnosed with HIV over the study period. Retrospective component will include secondary data, including HIV sequences and patient-related information, from 234 ART-naïve HIV patients diagnosed during the period of 1998-2012 and from 250 ART-experienced patients failing on therapy.

General eligibility criteria applicable to all specific aims to be accomplished include: 1) confirmed HIV infection, 2) age at least 18 years.

Specific inclusion criteria for estimating TDR (**specific aim 1a**) include: 1) HIV diagnosis within the 3 month of enrollment date 2) no previous exposure to antiretroviral drugs, 3) CD4 count >200 cells/mm³ and no AIDS-defining illness at the time of diagnosis. Study will enroll 150 eligible HIV patients entering clinical care at the National AIDS Center. We calculated range of samples sizes with the null hypothesis of no change in TDR since the previous survey (2.4%) and alternative hypothesis of increasing TDR to up to 10%. Sample size calculations indicated that 130 participants will be sufficient to accurately estimate the outcome. Because of emerging trends of HIV in MSM we will oversample this population to achieve the absolute number of homosexually infected men that is sufficient for drawing meaningful conclusions. Study procedures will include: informed consent, phlebotomy to obtain 5ml of blood, HIV genotyping and determination of TDR using drug resistance algorithm. Information on demographic, epidemiological and clinical characteristics will be extracted from the National HIV/AIDS Clinical Database.

Accomplishment of **specific aim 1b** will rely on secondary data from ART-experienced patients failing on therapy. We plan to analyze data from all HIV patients experiencing treatment failure at the time of study inception. Patients eligible for inclusion should meet the definition of treatment failure in accordance with National HIV/AIDS Treatment and Care Guidelines:

- The inability to achieve plasma HIV viral load <200 copies/ml 6 months to <50 copies/ml 12 months after commencing treatment in patients who remain on ART
- Detectable plasma viral load of >200 copies/ml after virologic suppression confirmed by two consecutive viral load measurements

All patients meeting the above referenced criteria receive HIV genotypic resistance testing as part of routine clinical care. Therefore drug resistance testing among patients with treatment failure will be performed at no cost to ISTC. Study will use sequences of viruses from these patients stored as FASTA files at the National AIDS Center. As of July 1, 2013 a total of 216 adult HIV patients received HIV genotypic resistance testing due treatment failure. We expect that data from at least 250 eligible patients will be available at the time of analysis.

Evaluation of trends in molecular epidemiology (**specific aim 2**) will be limited to treatment naïve persons. HIV patients with treatment failure will be excluded to avoid the influence of convergent evolution at antiretroviral drug-resistance mutations on the phylogenetic analysis. Analysis for specific aim 2 will include viral sequences from 150 ART-naïve newly diagnosed HIV patients and from 234 ART-naïve HIV patients available from previous surveys.

Laboratory methods

Specimens

5 mL of whole blood samples from each HIV infected patient will be collected in EDTA tubes. Tubes will be centrifuged at 1,000 to 2,000 $\times$ g at room temperature (15 to 25°C) for

15 minutes. Plasma samples will be aliquoted in 1.5 mL screw cap tubes and stored at -70°C for HIV resistance testing. As a part of a routine care, samples will be tested for CD4+ count and HIV viral load.

HIV-1 drug resistance

The ViroSeq™ HIV-1 Genotyping System (Abbott diagnostics, Wiesbaden, Germany) will be used for HIV drug resistance testing. The system detects mutations in the RT and protease regions of the pol gene and provides a report indicating genetic evidence of viral resistance.

The ViroSeq™ HIV-1 Genotyping System will be used to Genotype the entire HIV-1 protease gene from codons 1 to 99 and two-thirds of the reverse transcriptase (RT) gene from codons 1 to 335. A reverse transcription polymerase chain reaction (RT-PCR) followed by PCR will be carried out to generate an amplicon of 1.8 kb. The amplicons will then be purified using alcohol and PCR products run on 1% agarose gel against 2 mass ladders allowing for semiquantitation of DNA. The RT-PCR product band must have intensity equal to or greater than the 20 ng mass ladder band to ensure a high quality sequence. PCR products with intensity equal to or greater than the 20 ng mass ladder band will be diluted according to the band intensity and further used as a sequencing template for seven primers that generate an approximately 1.3 kb consensus sequence.

Sequencing will be performed on the 24 capillary automated 3500x/ Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) using data collection software v3.0 and sequence analysis software v5.3.

The ViroSeq HIV-1 Genotyping System Software v2.8 will be used to assemble the chromatographs from the six or seven primers that correspond to a single plasma sample into a single project, and to generate a contiguous sequence spanning the entire protease gene, and up to codon 335 of the reverse transcriptase (RT) gene. The consensus sequence will be compared to a known reference strain, HXB-2, to identify mutations present in the sample. The project format supports manual review and editing of the electropherogram data to generate a final consensus sequence for the HIV-1 protease and reverse transcriptase (RT) genes.

Finally, the ViroSeq software uses a proprietary algorithm to analyze the mutations and generate a drug resistance report. The algorithm determines the relative impact of mutations in the reverse transcriptase and protease open reading frames on the development of resistance to antiretroviral drugs.

The ViroSeq report has separate sections for Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and Protease Inhibitors (PIs). The mutations used in determining resistance are listed schematically along with the drug name in the report.

To determine the level of evidence for resistance to a given drug, the scores of the mutations that are present and pertinent to that drug are summed, giving a Total Score for that drug. For each drug, a particular codon position is only counted once using the highest mutation score among the mutations present at that codon position. A low Total Score (below 0.5) is interpreted as insufficient for resistance. A medium Total Score (between 0.5 and 1) is interpreted as possible resistance. A high Total Score (1.0 or more) is interpreted as resistant.

In addition, manually edited sequences from ViroSeq HIV-1 Genotyping System will be saved in FASTA format and will be submitted to web-based genotyping tool available at <http://hivdb.stanford.edu/> to determine the drug-resistance profile and subtype of each sample. Primary subtype assignment by <http://hivdb.stanford.edu/> will be used as a guide in further phylogenetic analyses.

Mutations, defined as substitutions as compared to a reference wild-type HIV-1 BLAV-1 sequence, will be classified according to the Stanford University algorithm. Prevalence of transmitted drug resistance will be estimated using the WHO surveillance drug-resistance mutations list,[37] while mutations listed by the International AIDS Society-USA (IAS-USA) Pane will be considered for treatment-experienced patients.[38]

Phylogenetic analyses

The consensus nucleotide sequences consisting of entire HIV-1 protease gene from codons 1 to 99 and two-thirds of the reverse transcriptase (RT) gene from codons 1 to 335 and saved as FASTA files will be exported to the web-based genotyping tool available at <http://hivdb.stanford.edu/>. Subtype assignment by Stanford HIV database program will be used as a guide in identifying relevant reference sequences in the Los Alamos National Laboratory HIV Sequence Database (<http://hiv-web.lanl.gov>). The study and reference nucleotide sequences will be assembled using the BioEdit package.[39] Sequences will be aligned using Clustal W with manual correction.[40] Nucleotide gaps will be assigned after amino acid conversion to maintain translation integrity, and gapped positions will be removed.

For every M-group subtype, at least one reference sequence from the Los Alamos Database, will be added. Maximum likelihood estimated distances will be used to construct neighbor joining phylogenetic trees. Bootstrap analysis will be performed with reliability estimated from 1,000 replicates. Neighbor joining phylogenetic tree will be reconstructed in PAUP* 4.0.[41]

Bayesian phylogenetic trees will be constructed using MrBayes under the same model conditions as described above with a sample frequency of 1000.[42] Bias introduced by convergent evolution due to the presence of drug resistant mutations will be avoided by repeating the analysis after removal of codons associated with transmitted drug resistance.

Recombination will be confirmed using RIP HIV Recombination Identification Program (<http://www.hiv.lanl.gov/content/sequence/RIP/RIP.html>).

Identification of transmission clusters

The initial identification of transmission clusters will be based on the NJ trees topology. All clusters of 3 or more patients, with a bootstrap value higher than 90, will be selected. Transmission pairs will be excluded since they do not necessarily represent sources of continuous onward transmission.[43] A more robust method, Bayesian inference, will be used to verify the clusters. Only clusters with a Bayesian posterior probability equal to 1 will be considered as transmission clusters.

National HIV Sequence Database

Specific aim 3 envisions establishment of national HIV sequence database. The purpose of the database is establishment of systematic approach for storing HIV sequences and drug resistance data. The data to be

entered in the database will include HIV sequence in FASTA format and HIV drug resistance report based on Stanford HIVdb Program (<http://hivdb.stanford.edu/>).

The sequence database will be integrated with the national HIV/AIDS clinical database. The former is the secure web-based application networking all HIV treatment and care provider institutions countrywide. The application allows for real time data entry including epidemiologic, demographic, clinical and laboratory data. The linkage between sequences and patient-level data will be ensured with the unique patient ID assigned to all HIV positive individuals at the time of diagnosis. Implementation steps will include: development of protocol for database, data entry and testing of the database. Fully operational database will be launched by the 4th quarter of project implementation.

Statistical analysis

In addition to the HIV drug resistance and subtype information, the following patient-related data will be collected: date of HIV diagnosis, date of sampling, sex, age at sampling, mode of HIV transmission, CD4 cell count and viral load at sampling, residence by country region. For treatment-experienced patients ART-related data will be collected, including date of ART initiation, ART regimens, CD4 cell count and viral load measurement at three time points – at the time of diagnosis, at ART initiation and at treatment failure. Selection of statistical methods will depend on the frequency of outcome measure. Binomial proportions with relevant confidence intervals will be calculated using exact methods. Comparisons will be tested using Pearson's chi-square or Fisher's exact tests as appropriate. All statistical analysis will be performed using SAS v9.2 (SAS Institute, Cary, NC, USA).

Research ethics

NCDC and National AIDS Center are well known for conducting scientifically rigorous and ethically sound research projects. The proposed study will be carried out in accordance with principles of Declaration of Helsinki.[44] Research protocol will be initiated only after securing approval from the local Institutional Review Board. Informed consent will sought from all patients enrolling in the study. Waiver for consent will be requested for secondary data to be utilized in the study. Appropriate measures will be undertaken to ensure confidentiality of data and persons. All investigators will be requested to complete recognized research ethics education course.

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7. Technical Schedule

	Quarter 1	Quarter 2	Quarter 3	Quarter 4	Quarter 5	Quarter 6	Person*days
Task 1					150 patients recruited		
Person*days	51	51	51	51	48		252
Task 2					Abstract prepared	Manuscript prepared	
Person*days	65	65	65	64	64	46	369
Task 3					Abstract prepared	Manuscript prepared	
Person*days	54	54	54	55	37	25	279
Task 4						Abstract and Manuscript prepared	
Person*days	16	19	19	22	42	54	172
Task 5						All available HIV sequence and related data are entered	
Person*days	45	49	49	49	49	47	288
TOTAL	231	238	238	241	240	172	1360

8. Personnel Commitments

8.1. Individual participants

Leading Institution: Short name

Category I (weapon scientific and technical personnel)

Name	Birth Year	Scientific Title	Weapon Expertise Ref.	Function in project	Daily rate (US\$)	Total days	Total grants (US\$)
Irma Burjanadaze	1972	MD	3	Manager	50	172	8600
Shota Tsanava	1957	MD, PhD	3	Lead expert/ Epidemiology and data management group	45	90	4050
Merab Mirtskhulava	1958	MS, PhD	3	Researcher/ Epidemiology and data management group	40	73	2920
Marina Chubidze	1952	MD	3	Researcher/laboratory group	35	74	2590
Roena Sukhaishvili	1971	MS	3	Researcher/laboratory group	35	120	4200
Total:						529	22360

Category II (other scientific and technical personnel)

Name	Birth Year	Scientific Title	Function in project	Daily rate (US\$)	Total days	Total grants (US\$)
Tsira Merabishvili	1963	MD	Researcher/Epidemiology and data management group	25	78	1950
Total:					78	1950

Participant Institution 1: Short name

Category I (weapon scientific and technical personnel)

Name	Birth Year	Scientific Title	Weapon Expertise Ref.	Function in project	Daily rate (US\$)	Total days	Total grants (US\$)
Tengiz Tsertsvadze	1946	MD, PhD	3	Scientific Leader	50	33	1650
Tsisana Shariava	1946	MD	3	Lead Expert	40	90	3600
Nanuli Burdglia	1949	MS	3	Researcher/Clinical group	34	78	2652
Total:						201	7902

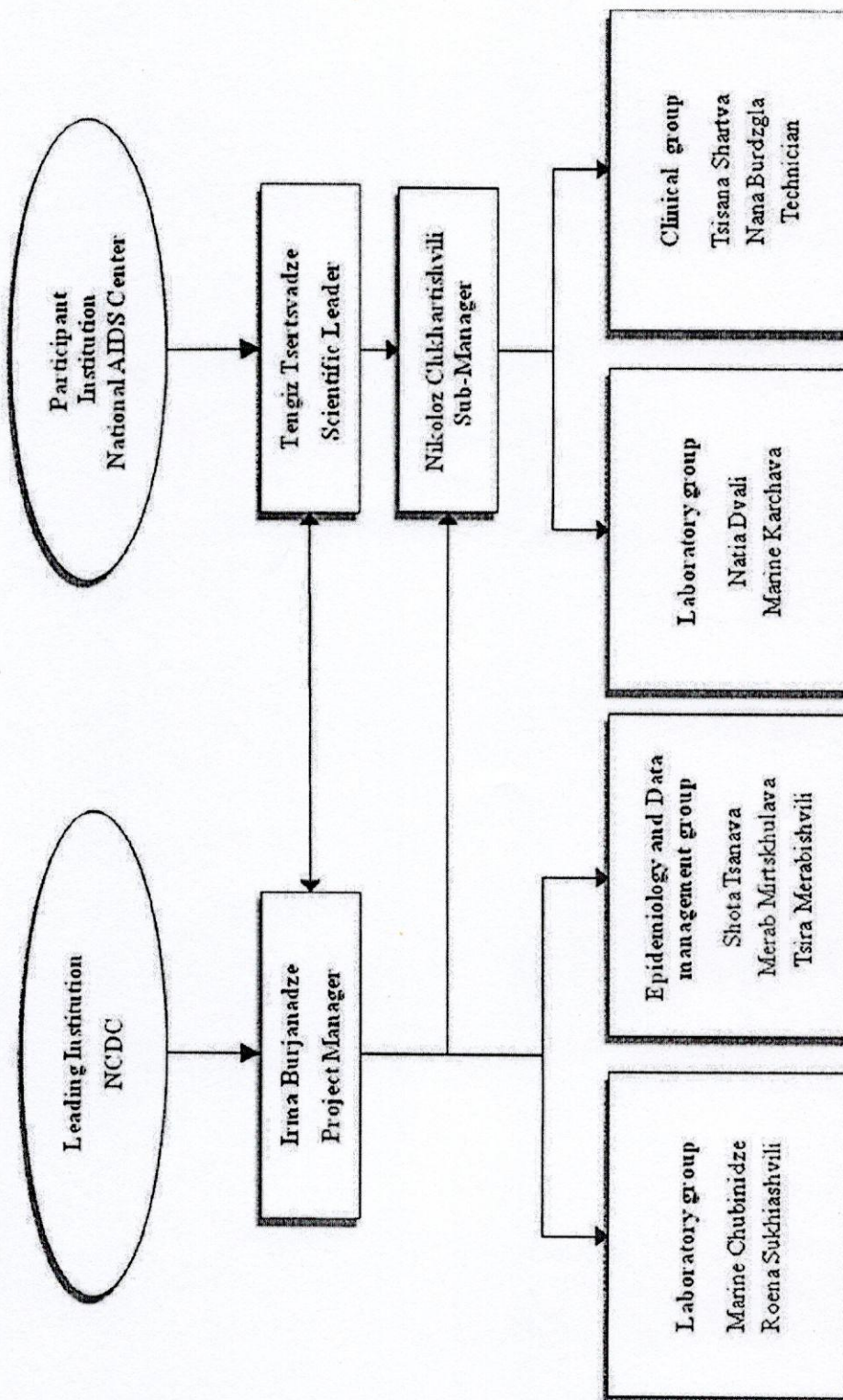
Category II (other scientific and technical personnel)

Name	Birth Year	Scientific Title	Function in project	Daily rate (US\$)	Total days	Total grants (US\$)
Nikoloz Chkhartishvili	1975	MD, MS	Sub-manager	40	144	5760
Natia Dvali	1977	MD	Researcher/Laboratory group	35	144	5040
Marine Karchava	1979	MD	Researcher/Laboratory group	35	144	5040
Total:					432	15840

Category III (participant personnel)

Name	Birth Year	Function in project	Daily rate (US\$)	Total days	Total grants (US\$)
Marine Mirziashvili	1972	Technician	20	120	2400
Total:				120	2400

8.2. Managerial responsibilities



9. Financial Information

TABLE 1

Estimated Aggregated Expenditures by Recipient

Category	Quarters 1 & 2		Year 1		Year 2		Total	
	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)
I Grant Payments:								
1.1 Category I		10408		21051		9211		30262
1.2 Category II		5880		11860		5930		17790
1.3 Category III		960		1920		480		2400
1.4 Category IV								
Total Grant Payments		17248		34831		15621		50452
2 Equipment:								
2.1 Capital Equipment								
2.2 Non-Capital Equipment								
Total Equipment								
3 Materials/Supplies		35240		35240				35240
4 Bank Fees		200		530		190		720
5 Other Direct Costs:								
5.1 Technological Energy								
5.2 Communications								
5.3 Subcontracts/Seminars								
5.4 Logistics/Customs		500		500				500
5.5 Other								
Total ODC		500		500				500
6 Travel:								
6.1 Internal ***								
6.2 Outside CIS				10140				10140
Total Travel				10140				10140

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Remarks: * (1) - Cash flow through Recipient Account
 ** (2) - Cash flow through ISTC
 *** Include Local and inside CIS travel

TABLE 1-1

Estimated Aggregated Expenditures by Leading Institution

Category	Quarters 1 & 2		Year 1		Year 2		Total	
	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)
1 Grant Payments:								
1.1 Category I		7590		15365		6995		22360
1.2 Category II		600		1300		650		1950
1.3 Category III								
1.4 Category IV								
<i>Total Grant Payments</i>		8190		16665		7645		24310
2 Equipment:								
2.1 Capital Equipment								
2.2 Non-Capital Equipment								
<i>Total Equipment</i>								
3 Materials/Supplies								
4 Bank Fees		90		250		100		350
5 Other Direct Costs:								
5.1 Technological Energy								
5.2 Communications								
5.3 Subcontracts/Seminars								
5.4 Logistics/Customs								
5.5 Other								
<i>Total ODC</i>								
6 Travel:								
6.1 Internal ***								
6.2 Outside CIS				3380				3380
<i>Total Travel</i>				3380				3380
Overhead/Retainage							848	
<i>Subtotals</i>		8280	0	20295	0	7745	848	28040
Totals		8280	20295		7745		28888	

Remarks: * (1) - Cash flow through Recipient Account

** (2) - Cash flow through ISTC

*** Include Local and inside CIS travel

TABLE 1-2
Estimated Aggregated Expenditures by Participant Institution 1

Category	Quarters 1 & 2		Year 1		Year 2		Total	
	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)
1 Grant Payments:								
1.1 Category I		2818		5686		2216		7902
1.2 Category II		5280		10560		5280		15840
1.3 Category III		960		1920		480		2400
1.4 Category IV								
<i>Total Grant Payments</i>		9058		18166		7976		26142
2 Equipment:								
2.1 Capital Equipment								
2.2 Non-Capital Equipment								
<i>Total Equipment</i>								
3 Materials/Supplies		35240		35240				35240
4 Bank Fees		110		280		90		370
5 Other Direct Costs:								
5.1 Technological Energy								
5.2 Communications								
5.3 Subcontracts/Seminars								
5.4 Logistics/Customs		500		500				500
5.5 Other								
<i>Total ODC</i>		500		500				500
6 Travel:								
6.1 Internal ***								
6.2 Outside CIS				6760				6760
<i>Total Travel</i>				6760				6760
<i>Overhead/Retainage</i>							2100	
<i>Subtotals</i>	0	44908	0	60946	0	8066	2100	69012
Totals		44908		60946		8066		71112

Remarks: * (1) - Cash flow through Recipient Account

** (2) - Cash flow through ISTC

*** Include Local and inside CIS travel

10. Equipment and Materials Summary

10.2. Materials Summary

TABLE 3

EQUIPMENT/MATERIAL SUMMARY					
MATERIAL SUMMARY for Project Agreement #G-2103					
					To be provided in kind ☒ To be purchased by recipient ☐
The ISTC will normally provide the most appropriate equipment that will perform the functions required; however, if very special reasons are given and explained in detail (Form PR-2E), the purchase of a particular make will be considered.					
Please list items in the order of their priority and put an 'X' in the column next to "Item no." if ISTC form PR-2E, "Data for a Single Equipment Item", has been completed for a given item and is attached.					
Item No.	DESCRIPTION OF ITEM	Date needed (quarter)	Qty	Unit cost (USD)	Amount (USD)
<i>Participant Institution 1: National AIDS Center</i>					
1	QiaAmp Viral RNA Mini kit, Qiagen, Cat#52904	1	2	1180	2360
2	ViroSeq HIV Genotyping Kit, Abbott, Cat#4j94-93	1	2	12580	25160
3	Sequencing Consumables kit, Abbott, Cat#4j94-92	1	2	475	950
4	PCR Clenup Kit, Abbott, Cat#4j94-93	1	2	125	250
5	POP-7 Performance Polymer, Applied Biosystems, Cat#4393708	1	2	470	940
6	Anode Buffer Container (pack of 4), Applied Biosystems, Cat#433927	1	2	275	550
7	Cathode Buffer Container (pack of 4), Applied Biosystems, Cat#4408256	1	2	380	760
8	3500xL Capillary Array 50 cm, Applied Biosystems, Cat#4404689	1	1	4270	4270
Subtotal:					35240
Estimated TOTAL COST:					35240

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10.4. Other Direct Costs Summary

TABLE 4

OTHER DIRECT COSTS SUMMARY						
OTHER DIRECT COSTS SUMMARY for Project Agreement #G-2103 To be provided in kind ☒ To be purchased by recipient ☐						
Detailed breakdown of Other Directs Costs to include planned activities under items 5.1, 5.2, 5.3, 5.4, 5.5 from Table 1 of the Project Agreement						
Item No.		DESCRIPTION OF ITEM	Date needed (quarter)	Qty	Unit cost (USD)	Amount (USD)
<i>Participant Institution 1: National AIDS Center</i>						
1	5.4	Logistics/Customs	1	2	250	500
Subtotal:						500
Estimated TOTAL COST:						500

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ANNEX II
General Conditions

Contents:

Part A	-	Implementation of the Work
Article 1	-	General Provisions
Article 2	-	Subcontracting
Article 3	-	Monitoring of the Work
Article 4	-	Reports
Article 5	-	Completion or Expiration of the Agreement
Part B	-	Payments
Article 6	-	Payments by the Center to the Recipient
Part C	-	Allowable Costs
Article 7	-	Accounting Principles, Allowable Costs and Transfer of Costs
Article 8	-	Direct Costs
Article 9	-	Overhead
Article 10	-	Costs not Allowed
Part D	-	Justification of Cost and Auditing
Article 11	-	Books of Account and Documentation
Article 12	-	Auditing
Part E	-	Information and Intellectual Property
Article 13	-	Definitions
Article 14	-	Promotion of Technology and Project Results
Article 15	-	Ownership
Article 16	-	Protection and Exploitation
Article 17	-	Reporting of Inventions
Article 18	-	Background Results
Article 19	-	Conflicting Agreements, Laws and Regulations



Annex II General Conditions

Part A - Implementation of the Work

Article 1 - General Provisions

1.1 The Recipient shall make best efforts to achieve the objectives of the Project and shall comply with all laws of the Republic of Georgia applicable to the Project. If in the course of project implementation deliverables are identified that may qualify under export control restrictions, the Recipient takes responsibility for obtaining the corresponding export licenses, in a timely fashion and operating in compliance with all Russian, CIS and International laws and regulations.

1.2 The Recipient shall, in particular, comply with all applicable laws and regulations related to safety.

1.3 The Recipient shall notify the Center's Project representative and the Partner without delay of:

- (a) any event or circumstance which may materially affect the Project, and
- (b) any proposal for significant changes of key personnel during the Project.

Article 2 - Subcontracting

2.1 Subcontracting shall require the advance written approval of the Center, with the concurrence of the Partner. However, approval shall not normally be given for subcontracting in any State that is not a Party to the ISTC Agreement unless the Center determines in writing that such subcontracting is essential for the Project.

2.2 The Recipient shall impose on a subcontractor the same obligations as apply to itself with respect to any rights of the Center or the Partner concerning the Project.

2.3 The provisions of Article 2.1 of this Annex shall not apply to Sub-Agreements pursuant to Article 3 of the Agreement or to orders for materials, equipment, and services which are incidental to or intended to facilitate the execution of the Agreement and placed in the normal course of business in accordance with the internal procedures and rules of the Recipient.

Article 3 - Monitoring of the Work

3.1 The Center shall:

- (a) Have access to portions of facilities where the Project is being carried out and to all equipment, documentation, information, data systems, materials, supplies, personnel and services which concern the Project for monitoring the progress of the Project as described in Annex I;
- (b) Be provided with technical and cost information concerning the management and progress of the Project requested at any time; and
- (c) Give the Recipient not less than 20 days advance notice of any intended on-site financial auditing or technical monitoring of the Project.

3.2 The Recipient has the right to protect those portions of facilities that are not related to the Project.

3.3 After completion or termination of the Project, the Recipient may utilize the facility or portion of the facility previously used for the Project for other work. However, all documentation and records including those associated with equipment, data systems, materials, supplies and services utilized for the Project must be maintained and available for review by the Center for up to two years following the Project's completion or termination.

3.4 The Recipient shall, if requested by the Center, participate and assist in meetings to review or evaluate the Project during the lifetime of the Project.

Article 4 - Reports

- 4.1 The Recipient shall submit the following reports, in a suitable quality to enable direct reproduction, to the Center and the Partner for approval:
- (a) A final report, in English and Russian, covering all the work, the objectives, the results and the conclusions, including a suitable summary of all these aspects; and
 - (b) Reports, as mutually agreed, prepared in a suitable form for publication and satisfactory to the Partner and the Center.
- 4.2 The Recipient shall submit any additional reports or any other deliverables specified in the Agreement.
- 4.3 The Recipient should clearly identify any reports or portions of reports that contain invention or business confidential information as defined in Part E of this Annex. The final report shall include a statement that all inventions Made during the performance of work under the Agreement have been reported to the Center and to the Partner, or if no inventions were Made, a statement to that effect. The Recipient also may include a suitable disclaimer in any report against possible claims by third parties.

Article 5 - Completion or Expiration of the Agreement

- 5.1 The Agreement shall be deemed to be completed on the approval by the Center and the Partner of the last deliverable required or last payment by the Center, whichever shall be the later.
- 5.2 Subject and without prejudice to the provisions in Part D of this Annex, the Recipient shall be deemed to have discharged its obligations with respect to the performance of the work after the approval of all the reports and any other deliverables required by the Agreement.

Part B - Payments

Article 6 - Payments by the Center to the Recipient

Payments of allowable costs other than the Center's in-kind contributions, the Center's grant payments to Individual Participants and overhead payments shall be made in accordance with the following principles.

- 6.1 Cost statements shall be expressed in US dollars unless otherwise specified in the Agreement. All payments by the Center shall be made in that currency unless otherwise agreed.
- 6.2 The financial contribution by the Partner through the Center shall be paid in installments as specified in Article 5 of the Agreement.
- 6.3 If the Center or the Partner considers that the work has not effectively been commenced within three months of the payment of the first advance, the Center may require the reimbursement of the advance together with any interest earned on the advance. Any reimbursements will be returned to the Partner account.
- 6.4 If on completion, cessation, or termination of the work, the payments made by the Center exceed the actual allowable costs, the Recipient shall promptly reimburse the difference to the Center. Interest may be added to this amount at the prevailing market rate as determined by the Center one month after the reimbursement date specified by the Center. Any reimbursements will be returned to the Partner account.
- 6.5 Subject to Article 12 of this Annex, periodic payments made against cost statements shall be considered as advances until acceptance of the appropriate deliverables, in accordance with Annex I, or, if no deliverables are specified, until acceptance of the final report.



Part C - Allowable Costs

Article 7 - Accounting Principles, Allowable Costs, and Transfer of Costs

7.1 The original estimates of expenditures set forth in Annex I may be adjusted by the Recipient between categories without the prior approval of the Center, except for reductions in personnel costs and increases in travel costs, and provided that the transfers do not fundamentally affect the scope or content of the Project.

7.2 The Recipient shall ensure that no unnecessary cost or unnecessarily high or extravagant cost is charged to the Agreement.

Article 8 - Direct Costs

8.1 Personnel

8.1.1 Personnel costs shall be separated into four categories as described in Annex I and reflected in the reporting form in Annex III. Even though some or all of these costs may be reimbursed by the Center through direct grant payments to the Individual Participants, the Recipient is responsible for certifying the time devoted to the Project by the Individual Participants and for maintaining necessary documentation to support such certification.

8.1.2 Personnel costs shall be charged to reflect the actual eight-hour days, or one-half days when appropriate, worked by personnel assigned by the Recipient to the Project in accordance with Annex I. Work periods of less than four hours may not be charged.

8.1.3 Personnel costs for a specific period of time may not be charged to this Project if reimbursement (except regular employment salary) is being received from other sources for the same period of time.

8.1.4 The Project Manager may increase or decrease the time commitments of personnel by up to 10 percent during one year of any individual without approval of the Center, but may not change the daily rate without approval by the Center. The Project Manager may request more significant changes in the personnel commitments, including changes in the names of the personnel, at the beginning of each quarter with a brief explanation of the reasons for the changes. In unusual situations, the Project Manager may request changes during the quarter. The Center, in consultation with the Partner, will respond promptly to such requests. Changes in scientific personnel must provide for the new participants to have technical credentials and weapons experience comparable to those of the personnel they replace.

8.1.5 The Center will not reimburse personnel costs associated with holidays, annual vacations, overtime, or sick leave. Such additional costs, if any, are the responsibility of the Recipient.

8.1.6 The Project Manager shall ensure that the scheduling of annual leave by the Individual Participants does not interfere with accomplishment of the Work Plan in Annex I.

8.1.7 The Recipient is responsible for any medical expenses or compensation claims for injuries or other losses for personnel working on the Project which are directly or indirectly related to the Project.

8.1.8 Individual daily records of time devoted to the Project must be signed by all personnel assigned to the Project, and all records must be certified at least monthly by the Project Manager and for the Project Manager by another appropriate senior employee of the Recipient.

8.2 Equipment

8.2.1 Equipment shall be categorized as indicated in the reporting form in Annex III.



8.2.2 The cost of equipment used in the Project which is purchased, fabricated, or leased after the Operative Commencement Date may be charged as a direct cost. The total leasing cost of any piece of equipment shall not exceed the cost which would have been allowable for its purchase.

8.2.3 Notwithstanding Article 4.5.1 of the Agreement, the Center will retain the title to all the equipment provided to or procured by the Recipient using Center funds regardless of the acquisition per item cost of the equipment. The final decision of possible transfer of the title shall be taken by the Center, in consultation with the Financing Party by the time of completion, termination or cessation of the Project taking into account the specific legal, institutional and other factors in effect in the state of the Recipient at that time.

8.3 Materials

The costs of required materials shall be allowable costs. They shall be categorized as raw materials, laboratory supplies, safety devices and protective gear and other as indicated on the reporting form in Annex III.

8.4 Other Direct Costs

8.4.1 Other direct costs shall be categorized as indicated in the reporting form in Annex III.

8.4.2 Costs incurred by the Recipient in using its internal resources for performance of the Agreement such as costs associated with (a) testing facilities, (b) computer services, (c) special test equipment, (d) dedicated security services, and (e) dedicated accounting services, but excluding items covered by Article 9 of Annex II, may be charged as direct costs through valid cost allocation formulas approved by the Center to the extent such costs contribute to the Project, provided such facilities and services are open to access for monitoring and auditing in accordance with Article 9 of the Agreement. If costs incurred by the Recipient are not charged as direct costs, they may be presented as in-kind contributions of the Recipient.

8.5 Travel and Per Diem for the Recipient

Travel and per diem within the CIS shall be charged in accordance with the internal rules of the Recipient which are subject to approval by the Center. International travel shall be provided by the Center in accordance with Article 4 of the Agreement.

8.6 Sub-Agreements and Subcontracts

8.6.1 Subject to Article 2 of this Annex, costs of subcontracts shall be allowable costs and shall be included as discrete entries in the appropriate categories on the reporting form of Annex III. If the subcontractor is a scientific institution engaged in a sub-agreement pursuant to Article 3 of the Agreement, costs are allowable only to the extent that they would be allowable if incurred directly under the Agreement. In selecting a subcontractor other than a scientific institution pursuant to Article 3 of the Agreement, the Recipient shall compare prices and quality of several subcontractors and choose the most cost-effective offer. For any subcontract costing more than the equivalent of \$25,000, the Recipient shall organize a bidding process. For any subcontract costing between \$10,000 and \$25,000 (equivalent) written quotations shall be obtained from three sources to the extent possible.

8.6.2 Should the Recipient enter into a sub-agreement with a scientific institution pursuant to Article 3 of the Agreement, the reporting form in Annex III shall include the costs incurred pursuant to the sub-agreement which shall be supported by detailed information.

Article 9 - Overhead

A fixed payment may be charged with respect to overhead which covers items such as general administration, institutional management, depreciation of buildings and general equipment, maintenance of building and grounds, telephones, heating, lighting, electricity for the buildings and general staff training.

The payment shall not exceed 10% of the direct Project costs, excluding equipment, travel and subsistence.



Since the overhead will be retained by the Center until acceptance of the final report, the Recipient need not include this item on the reporting form in Annex III.

Article 10 - Costs Not Allowed

Allowable costs shall not include, among others:

- any profit;
- any contributions to pension, medical, or other social funds;
- any provisions for possible future losses or liabilities;
- any taxes, including profit tax, value added tax, personal income tax, and local taxes, as well as any other tariffs, dues, custom duties, import duties, fees, or other imposed taxes or similar charges;
- any costs allocatable to other projects.

The Center will determine the use of any interest earned from funds provided by the Center or return on investment of such funds. Such interest or return on investment must be reported to the Center.

Part D - Justification of Costs and Auditing

Article 11 - Books of Account and Documentation

The Recipient shall maintain, in accordance with the accounting practices set forth in the Agreement, proper books of account and appropriate documentation, such as invoices and time sheets to support and justify the costs reported. These shall be made available for audits by the Center during the period of the Project and for a period of up to two years following the Project's completion or termination.

Article 12 - Auditing

12.1 Cost statements are subject to verification even after the Center has reimbursed costs. The Center has the right pursuant to the ISTC Agreement and ISTC Statute to carry out on-site auditing of all activities of the Project. The Recipient will be given not less than 20 days notice of any intended audit. For the purposes of the audit, the Recipient shall make accessible all portions of facilities, equipment, documentation, information, data systems, materials, supplies, personnel and services related to the Project.

12.2 The Recipient has the right to protect those portions of facilities that are not related to the Project.

12.3 The Recipient shall maintain all documentation and records including those associated with equipment, data systems, materials, supplies and services utilized for the Project and shall make such documents, records and, to the extent possible, personnel available for auditing for a period of up to two years following the Project's completion or termination.

12.4 The Center shall have the right to select Courts of Auditors or other organizations or individuals to carry out audits of the Project; they shall be entitled to the same rights, should they choose to exercise them, as the Center with respect to access to, and verification of, any document under the Agreement for the purpose of any audit.

Part E - Information and Intellectual Property

Article 13 - Definitions

13.1 "Intellectual Property" includes inventions, patents, copyrights and other forms of protection provided by statutes, such as, industrial designs, design patents, mask works, and trademarks, and has the meaning defined in Article 2 of the Convention Establishing the World Intellectual Property Organization, done in Stockholm on July 14, 1967, which states: "Intellectual Property shall include the rights relating to:

- literary, artistic and scientific works,
- performances of performing artists, phonograms, and broadcasts,
- inventions in all fields of human endeavor,

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- scientific discoveries,
 - industrial designs,
 - trademarks, service marks, and commercial names and designations,
 - protection against unfair competition,
 - and all other rights resulting from intellectual activity in the industrial, scientific, literary or artistic fields."

13.2 "Information" includes technical data and computer software and means recorded data of any kind of a scientific or technical nature, regardless of the form or method of recording, and capable of being read by a human being or processed by a machine.

13.3 "Foreground Results" means Foreground Information and Foreground Intellectual Property.

13.4 "Foreground Information" means Information, including all kinds of results, generated in the execution of this Agreement.

13.5 "Foreground Intellectual Property" means rights in Intellectual Property generated in the execution of this Agreement by the Recipient or any person employed or engaged by the Recipient.

13.6 "Background Results" means Background Information and Background Intellectual Property.

13.7 "Background Information" means Information, excluding Foreground Information, owned or controlled by either the Recipient or Partner in the same or related fields as the research under this Agreement and generated outside this Agreement.

13.8 "Background Intellectual Property" means rights in Intellectual Property, excluding Foreground Intellectual Property, owned or controlled by either the Recipient or Partner in the same or related fields as the research executed under this Agreement and originating outside this Agreement.

13.9 "Business Confidential Information" is also known as trade secret information and means technical, commercial or financial information, which:

Has been held in confidence by its owner;

Is not generally known or available from other sources;

Has not been made available by its owner to other parties without an obligation concerning its confidentiality;

Has not been independently developed by the receiving party; and

Is not available to the receiving party without obligations concerning confidentiality.

13.10 "Invention Information" is Intellectual Property which is to be protected by a patent and on which a patent has not been filed.

13.11 "Made," when used in relation to any invention, means the conception or first actual reduction to practice of such invention.

13.12 "Unlimited rights" means the right to use, modify, reproduce, perform, display, release, or disclose Information in whole or in part, in any manner, and for any purpose whatsoever, and to have or authorize others to do so.

Article 14 - Promotion of Technology and Project Results

Confidentiality

14.1 Subject to Article 4.1(c), all reports or portions of reports properly marked as Invention Information or Business Confidential Information by the Recipient in consultation with the Partner shall be protected from public

dissemination unless otherwise agreed by the Recipient and the Partner. Invention Information is treated as Business Confidential Information until a patent application has been obtained unless such information so disclosed is or becomes legitimately available to the receiving Signatory Party through other means or sources without any covenant as regards its confidentiality. Nevertheless, Business Confidential Information may be disclosed if the disclosure is required by law, regulation, or court order.

14.2 Subject to any obligations under this Agreement and in accordance with applicable laws and regulations, the Signatory Parties agree to keep confidential any Invention Information or Business Confidential Information communicated to them by other Signatory Parties or third parties in relation to the execution of this Agreement, unless such information so disclosed is or becomes legitimately available to the receiving Signatory Party through other means or sources without any covenant as regards its confidentiality. Nevertheless, Business Confidential Information may be disclosed if the disclosure is required by law, regulation, or court order.

Technology Promotion

14.3 The ISTC shall be entitled to publish general information on this Agreement including the identities of the Recipient and Partner, the title and objective of the Agreement, its estimated costs and duration, and the names of managers and laboratories where the research is being carried out.

14.4 Each Signatory Party agrees to submit to each other Signatory Party for review and approval a copy of any proposed publication of Foreground Information at least thirty days before such publication.

14.5 Any public communication or publication concerning this Project will acknowledge the Recipient, the Partner and the cooperative support of the ISTC.

14.6 Subject to the restrictions of Article 14.1, each Party to the ISTC Agreement (hereinafter referred to as the "ISTC Party") and the ISTC have a non-exclusive, irrevocable, royalty-free license with the right to sub-license in all countries to translate, reproduce and publicly distribute scientific and technical journal articles, reports, and books directly arising under this Agreement. All publicly distributed copies of a copyrighted work arising from cooperation under this Agreement shall indicate the names of the authors of the work, unless an author explicitly declines to be named.

Article 15 – Ownership of Intellectual Property and Foreground Information

15.1 In accordance with the ISTC Statute, except for inventions created by United States Government employees, all rights worldwide to Intellectual Property arising under this Agreement, including patent protection for industrial property, belong to the Recipient (or its designee), which has the responsibility for providing adequate protection of such Intellectual Property. The Recipient and the Partner have agreed to protect and allocate such Intellectual Property among each other as specified in Article 16 below. Rights to inventions made by United States Government employees or made in Partner's laboratory shall be determined by the United States.

15.2 All rights worldwide to Foreground Information arising under this Agreement belong to the Recipient (or its designee). The United States Government, as represented by Partner, is granted a non-exclusive, irrevocable, royalty-free, worldwide license of unlimited rights in Foreground Information.

Article 16 - Protection and Exploitation

16.1 Intellectual Property Rights (IPR) Allocation

- (i) The work conducted under this project is expected to generate new intellectual property by the Recipient and the Partner;
- (ii) The protection and allocation of intellectual property created or furnished in the course of the cooperative research activities pursuant to this Agreement shall be provided in accordance with the Articles 16.2, 16.3, 16.4, 16.5, 16.6, 16.7, 16.8, 16.9 of the Annex II.
- (iii) Any publications or presentations of information developed by the project participants shall acknowledge their funding support and shall be cleared by the institutions involved according with the existing procedures. Joint work is expected to result in joint authorship of publications.

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- (iv) The development of any new commercial products and commercialization of results are not expected to be the issue during the term of the project
 - (v) However if this proves otherwise, the Recipient and its Partner agree to notify one another as well as other Parties of the Agreement in a timely fashion of any invention or copyrighted works arising under this Project and to seek protection for such intellectual property in a timely fashion.
 - (vi) The Recipient and the Partner shall be responsible for the maintenance, protection and preservation of all intellectual property during the term of the project

16.2 Ownership and Non-exclusive License: With the exception of inventions made by employees of the United States Government, the Recipient owns worldwide rights to Intellectual Property arising under this Agreement. The United States Government as represented by the Partner shall determine the rights in inventions made by United States Government employees or made in U.S. Government facilities. The United States Government, as represented by partner, is granted in all Intellectual Property arising under this Agreement a non-exclusive, irrevocable, royalty-free, worldwide (except for the territory of the United States) license to practice or have practiced for or on behalf of the United States. Upon the request of the Partner (or its designee), the Recipient entity (or its designee) shall enter into negotiation with United States commercial entities for licenses for commercial purposes on fair and reasonable terms in territories other than the United States in all Intellectual Property arising under this Agreement.

16.3 Commercialization in the United States: Upon request by Partner, the Recipient shall assign to the Government of the United States as represented by Partner, subject to a royalty-free, irrevocable non-exclusive license to the recipient, the entire right, title, and interest in any Intellectual Property in the United States, including inventions, patents on inventions, and copyrights arising under the Agreement. The Government of the United States will obtain and pay for all costs of obtaining patent protection in the United States on those inventions that the Recipient and Partner mutually agree to obtain patent protection in the United States (See Article 16.6). All uses of the Intellectual Property by or for the Government of the United States are royalty free. When the Government of the United States as represented by Partner or Partner's designee, negotiates and executes a license for commercial purposes to use Intellectual Property within the territory of the United States, which are purposes other than those by or for the Government, compensation will be sought for all uses of the Intellectual Property.

16.4 Compensation for inventors: In accordance with the policies of the Partner, which provide that the inventive entity shall receive at least 15% of royalties received, the inventors will receive a portion of the royalty income. The remaining royalties will be applied to cover or offset expenses incurred in obtaining and maintaining patent protection; and any remaining royalty income, after paying patent expenses, will be shared equally between the Recipient and Partner. However, the inventor, or inventors as a group, will always receive at least 15% of the total royalties received each year in accordance with the policies of the Partner.

16.5 Disclosure of inventions within two months: A written disclosure of invention will be provided by the Recipient (or its designee) to the Partner within two months of the date on which the invention is Made. See Article 17.2

16.6 Election to file patent applications within six months: The Recipient will notify Partner within six months of reporting an invention of each territory, except for the territory of the United States, in which the Recipient elects to protect the invention through patenting. In the territory of the United States, election to file will be by mutual agreement of the Recipient and Partner, and if the parties are unable to agree within eight months of reporting an invention and the Partner has not requested assignment under 16.3, either the Recipient or Partner may elect, by notifying the other party, to obtain patent protection in the United States and the party electing to file will pay all patent costs and will not share royalties with the Party not electing to file. If the Recipient files for a patent in the United States, the Government of the United States, as represented by Partner, shall have a non-exclusive, irrevocable, royalty-free license to practice or have practiced for or on behalf of the United States. See Articles 16.3 for patent costs and 17.3.

16.7 Filing of patent applications: The Recipient will file the first patent application within twelve months of reporting the invention. Partner has right to file patent applications in the countries in which the Recipient does not



elect to file. If the Recipient does not elect to file within eight months of the date on which the invention is Made, the Partner may file applications in all countries in which the Recipient does not elect to file, and the Recipient will assign title to the invention to the Partner in those countries in which the Partner has filed. The Recipient will retain a non-exclusive irrevocable, royalty free license in the territory where the Partner has filed. See Article 17.3

16.8 Exploitation of Results: The Technology Implementation Plan required by Article 8.2 of the Project Agreement shall contain a listing of all inventions Made under the Agreement, the status of pending patent applications, or patent numbers, licenses granted and in negotiation, and relate the commercial results of the research performed under the Agreement with the anticipated commercial results and intellectual property rights described in the proposal submitted for the Agreement.

16.9 The Recipient will grant to the United States Government, as represented by Partner, under reasonable terms and conditions the right to use by or for the Government Background Results owned by the Recipient which are necessary for the Partner to exploit Foreground Results, provided that the Recipient is free to disclose such Background Results, that no major business interests of the Recipient oppose the granting of such right, that in making this opposition such interests are not abusively restricting the exploitation of such right and that granting such right is not restricted by the law or obligations to a third party. The Recipient will notify the Partner, with factual statements in the next monthly technical report, of all situations where: the Recipient is not free to disclose such Background Results; or a major business interest opposes the granting of such right to such Background Results; or the disclosure of such Background Results is restricted by law or obligations to a third party.

Article 17 - Reporting of Inventions

17.1 The Recipient will disclose to the Partner and the ISTC in an ISTC-approved form every invention Made under this Agreement within two (2) months of the date on which such invention is Made. These disclosures must be in sufficiently complete technical detail to convey a clear understanding, to the extent known at the time of the disclosure, of the nature, purpose and operation of the invention.

17.2 The Recipient and the Partner will notify the ISTC of each territory in which each (or their designees) decides to protect inventions through patenting within six (6) months of the reporting of such inventions in accordance with Article 17.1 above.

17.3 The Recipient and the Partner will file patent applications in each territory in which each (or its designee) decides in accordance with Article 17.2 above to protect each invention through patenting. The first patent application will be filed in the territory where the invention was Made within twelve (12) months of reporting the invention in accordance with Article 17.1 above. The remaining patent applications will be filed in the other territories within respective time periods to ensure that the priority date of the first patent application is obtained for these later filed applications. The Recipient and the Partner will provide each other and the ISTC with copies of all patent applications each (or its designee) files.

Article 18 - Background Results

The Recipient and the Partner have identified and agreed that the following Background Results may be used in the performance of work under this Agreement and may be needed to practice any Foreground Results of this Agreement:

Recipient's Background Results: *none*.

Partner's Background Results: *none*.

Recipient and Partner represent that the above-identified Background Results are available for licensing as of the effective date of this Agreement.

Article 19 - Conflicting Agreements, Laws and Regulations

19.1 Recipient certifies that it has not and will not enter into any agreement with a third party that grants to the third party rights to Foreground Results that may affect the exploitation or commercialization of Foreground Results received by the Partner under this Agreement.

19.2 Recipient shall notify the Partner and the ISTC of any restrictions by government laws or regulations which may materially and adversely affect the rights necessary for the performance of the work or the exploitation and commercialization of Foreground Results.

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ANNEX III
Formats for Progress and Cost Reports

1. Format for Technical Reports

Quarterly reports shall specify the progress, any actual or proposed deviations and modifications to the Work Plan in Annex I, and the results obtained. The reports shall contain sufficient information to enable assessment of the progress and cooperation within the Project. The details of the Annual Report shall be agreed upon at an appropriate time by the Recipient and the Center's Project representative. A suggested format for quarterly reports is as follows:

- I. Summary of Technical Progress (By task in the Work Plan)
- II. Milestones Completed
- III. Summary of Personnel Commitments
- IV. Major Equipment Acquired
- V. Description of Significant Travel
- VI. Current Technical Status (on schedule, behind schedule, ahead of schedule)
- VII. Delays, Problems, Suggestions
- VIII. IPR Annex

The quarterly report should be between three and five pages (single space).

2. Financial Forms

(The templates for reports are to be provided separately by the Center.)

3. Submission Dates for Technical and Financial Reports:

Technical and Financial reports are due two weeks after the end of each fiscal year quarter:

- May 15
- August 15
- November 15
- February 15

Additional time (two weeks) shall be granted for reconciliation (adjustments) of end-of-year balances.

**ANNEX IV
DISCLAIMER**

It is understood and agreed to by the Recipient of this ISTC project that:

The project funding commitment of the ISTC is subject to and limited by the funds which are actually available by the ISTC Financing Party(ies) for this project;

The funding for each project comes from ISTC Financing Parties and/or Partners who might make their ISTC financial contribution in whichever currency considered appropriate;

As a matter of practice, the ISTC at present signs all project agreements in a single currency, the US dollar;

The project support given to this project by the ISTC Financing Party(ies) and/or Partners of the ISTC may be affected by causes, including currency fluctuation, which may require adjustments in the project budget.