REQUEST FOR LETTER OF INQUIRY

NEW BIOMARKERS FOR HIV INCIDENCE MEASUREMENT

DEADLINE: FRIDAY, MAY 18, 2012, 10:00 AM PST

HIV DIAGNOSTICS, GLOBAL HEALTH

BILL & MELINDA GATES *foundation*

About the Bill & Melinda Gates Foundation

Guided by the belief that every life has equal value, the Bill & Melinda Gates Foundation works to help all people lead healthy, productive lives. In developing countries, it focuses on improving people's health and giving them the chance to lift themselves out of hunger and extreme poverty. In the United States, it seeks to ensure that all people—especially those with the fewest resources—have access to the opportunities they need to succeed in school and life. Based in Seattle, the foundation is led by CEO Jeff Raikes and co-chair William H. Gates Sr., under the direction of Bill and Melinda Gates and Warren Buffett.

HIV Program Goal

The Bill & Melinda Gates Foundation's HIV strategy is aimed at reducing new HIV infections and reducing the burden of disease in developing countries, where the epidemic represents one of the most serious health and development challenges. Tremendous progress has been achieved on HIV over the past decade. Our strategy is to build on that progress by strengthening HIV prevention and helping ensure that HIV programs are as efficient and effective as possible.

The Challenge

HIV incidence is the estimated rate of new infections in a population. It is the primary outcome measure for most HIV prevention activities and a key element in the design of clinical trials to evaluate new prevention interventions. From a public health perspective, HIV incidence estimates in different population subsets can help target interventions for maximum cost-effectiveness and can provide valuable inputs to assessments of program impact. Small decrements in HIV incidence can have profound effects over time on HIV epidemics, and the precision with which incidence must be measured to determine incremental progress in containing the pandemic poses a daunting technical challenge.

Current methods to measure HIV incidence rely on statistical modeling, longitudinal cohort studies, or the use of biological assays. A reliable biological assay has the potential to require less time, labor, and cost than the other methods. Biological assays aim to identify a biomarker that can distinguish recent from chronic or late-stage infection. Many of these assays are based on measuring the strength or amount of antibody binding to specific viral targets.

These currently available biological assays are often inaccurate for several reasons:

1. **High false recent rates (>5%) for persons who are not recently infected yet test as recently infected.** Late-stage disease, anti-retroviral use, and long-term survival can be associated with immune responses that are similar to those during early stages post infection, causing high false recent rates. In addition, differences in viral sequences from different geographies may contribute to variable responses of currently available assays.
2. **Short mean duration of recency.** The mean time window that the ideal assay identifies a person as recently infected should be 6-12 months. The combination of the duration of recency and the false recent rate impact the sample size required to adequately measure incidence and

longer durations coupled with low false recent rates will be required for a biological incidence assay to be feasible. However, most currently available assays have an undefined mean duration of recency or one that is too short for feasibility.

3. **Not feasible for use in surveillance setting.** For large-scale surveys to take place in developing countries, biomarkers in tissue samples must be stable enough to withstand transportation to a centralized laboratory facility. While most currently available assays fit this criteria, some new concepts in consideration do not.

Goal of This Request for Letter of Inquiry

New biomarkers for HIV incidence assays that reliably identify recently infected individuals for population incidence measurement need to be discovered. The goal of this Request for Letter of Inquiry is to solicit inquiries from investigators to identify novel biomarkers that can be used effectively to measure HIV incidence. We are looking for biomarkers that could be used alone or in combination and that are at the initial development stage.

What We Are Seeking

Candidate biomarkers can be viral or host-derived and have the potential to be developed into a product that meets the target product profile specified below. Informed by statistical modeling and user requirements the minimal and optimal target product profile (TPP) for an incidence assay is defined below:

	Target Product Profile	
Specification	Minimum	Optimal
Intended use	Population incidence measurement – not for individual use	Population incidence measurement and individual use
Target population	Specific to a population or clade	Appropriate for all clades
Mean duration of recency	4 months	1 year
False recent rate	2%	<1%
Multi-assay algorithm	Multiple assay algorithm	Single assay
Sample type	Previously frozen blood plasma or serum	Previously frozen blood plasma or serum; blood spots; or other easily obtainable specimen (e.g. saliva, breath, or urine) that is able to withstand several hours of transport in developing country conditions
Sample collection method	Venipuncture	Finger prick
Infrastructure required	Centralized laboratory facility (clean water and electricity required)	None (all reagents and materials are contained in assay kit)

	Target Product Profile (Continued)	
Specification	Minimum	Optimal
Storage conditions	4 – 25 degrees C	Up to 35 degrees C; robust to frequent temperature cycling; high humidity
Training required	Laboratory technician can be proficient with one week of training based on proficiency testing	One day or less training would allow any health care worker to run the assay
Regulatory requirements	None; product is for research use only	GMP or ISO 13485 or equivalent; FDA approval
Shelf life	12 months	>24 months

Applicants must provide a clear description of the methods of testing and analysis of the candidate biomarkers.

The evaluation pathway for a new biomarker can include multiple phases: I) development phase where either hypothesis testing or exploratory work is conducted on small unblinded sample sets; II) qualification phase, where rudimentary assay performance is assessed as qualification for subsequent evaluation; III) evaluation, where the false recent rate and mean recency duration is defined in multiple subtypes to determine if the biomarker(s) meets TPP; IV) validation, where the biomarker(s) is used in a field setting and compared to an alternate incidence measurement. The purpose of this request is to fund the development and qualification phases, prior to consideration for evaluation or validation. To make the results of such analysis comparable to that of other putative biomarkers, a standardized set of samples forming development and qualification panels will be made available to funded investigators upon request. These will include blood products, urine, oral fluid, hair, and stool. Descriptions of the panels can be found at http://www.incidence-estimation.com/page/the-cephia-repository.

The Bill & Melinda Gates Foundation is willing to invest a total of $3M for establishing proof-of-concept of a novel biomarker, or set of biomarkers for the measurement of HIV incidence. Individual proposals should not exceed $1M in total cost and should clearly identify decisions and endpoints that fit within the timeframe of 36 months or less.

Proposals submitted for consideration must have a well-developed work plan using clearly defined endpoints, criteria for down-selection, and measures of success. Successful applicants will present a strong rationale based on preliminary published or unpublished data for the selection of candidate biomarkers to be evaluated or methods for non-hypothesis driven exploration. Successful applicants will also present a sound statistical justification of the sample size, evaluation criteria, and analysis plan.

Examples of projects that would be considered for funding

- Novel conceptual approaches such as the measurement of gut integrity or viral components in hair
- Screening approaches to identify novel classes of biomarkers (e.g., metabolites, chemokines, transcription changes, etc.) that could be used for incidence measurement
- Applications of innovative technologies that can make the detection of novel biomarkers feasible (e.g., high-throughput, highly parallel, rapid technologies) taking into consideration the target product profile
- Screening approaches to identify biomarkers in novel sample types (e.g., urine, saliva, throat washes, hair, stool)
- Statistical analysis of existing data demonstrating a novel conceptual approach

For this initiative, we will not consider funding

- Continued adaptation or evaluations of new combinations of currently available diagnostic assays
- Assays solely dependent on assessing viral diversity
- Studies that propose to define the window period or false positive rate of existing diagnostic assays
- Assay principles and procedures that do not have the potential to conform to the broad guidelines outlined above

Program Structure

A. Application Instructions and Review Process

A Letter of Inquiry (LOI) in response to this request should be submitted no later than May 18, 2012, 10:00 AM PST. The Bill & Melinda Gates Foundation will review the LOIs using the Evaluation Criteria outlined below. In July 2012, the foundation will invite a select number of applicants to submit full proposals by August 2012. These time periods are subject to change if the volume of applications exceeds the number expected and thus requires additional time for processing and evaluation. This LOI Request and any invitation by the foundation to submit full proposals are not offers by the foundation to invest or partner. The foundation assumes no responsibility for cost incurred in responding to this LOI Request and any further invitations or communications from the foundation. All responses shall become the property of the foundation upon submission. Moreover, the LOI Request may be amended or withdrawn at any time and copies of the amendments or withdrawals of the request will be sent to all those submitting an LOI.

If the foundation receives and responds to clarifying questions regarding this LOI Request, the questions and answers will be made available to all parties to ensure fairness.

All applicants will be notified by email in a timely manner of any change to the dates for notification and proposal deadline. Instructions on the preparation of full proposals will be provided to selected

applicants. Due to expected high volumes, the foundation will not be able to provide individual feedback for LOIs not selected to submit full proposals. The foundation may use external reviewers to assess the merit of proposals and those reviewers will be provided copies of the LOIs; final selection decisions will be made by the foundation.

Letters of inquiry must be submitted electronically, using the forms and process described at the following address:

https://unison.gatesfoundation.org/Applicant/_layouts/Portal/Applicants/ApplicationForm.aspx?RequestId=c32b760b-0872-e111-bafd-0019b9f2848b

Application Schedule Event	Key dates and deadlines
Letters of inquiry (LOI) accepted	April 6, 2012
Application deadline for Letters of Inquiry (LOI)	May 18, 2012, 10:00 AM PST
Invitation for submission for full proposals	July 9, 2012
Application deadline for full proposal	August 6, 2012, 10:00 AM PST
Response to applicants	September 14, 2012
Anticipated start date	November/December 2012

B. Evaluation Criteria

1. **Significance**. Is the approach likely to deliver novel biomarker(s) for HIV incidence measurement? Do the biomarkers proposed have the potential to be readily developed into a feasible assay? Do the biomarker(s) proposed represent an important advance in the field through an innovative approach, robust analysis plan, and/or potential to test an as yet unproven candidate biomarker?

2. **Approach.** Are the conceptual framework, design, methods, and analyses innovative, adequately developed, statistically robust, and appropriate to the aims of the proposal? Does the application acknowledge potential problem areas and consider alternative tactics? Is the likelihood of successful project completion high? Are the proposed timeline and milestones appropriate, feasible, and technically sound?

3. **Best Value.** Proposals will be evaluated for the cost relative to the complexity of the proposed work and the degree of risk and advancement proposed. Proposals that have execution plans which represent particularly thoughtful and efficient use of resources will be preferred over proposals representing comparable efforts that do not represent the same value for the investment.

4. **Organizational and Investigator Capability.** Is the research team appropriately trained, experienced, and positioned to carry out this work? Is there strong evidence of substantive organizational capability and commitment? Does the environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environments

including partnerships with industry or employ useful collaborative arrangements? While the foundation fosters collaborations and formation of consortiums, these will have to be set up by the proposer, as this will not be done by the foundation.

C. Eligibility Criteria

Applicant organizations must be individual non-profit organizations, for-profit companies, or other recognized institutions that can successfully execute the activities in their technical area.

D. Allowable Costs

Grant funds may be used for the following costs. While not necessary for the LOI, full proposals will require budget estimates according to these allowable categories: personnel, required travel, supplies, contracted services, sub-grants, and consultants. Partial or full support for equipment may be requested subject to the following circumstances. Use of any equipment purchased with grant funds is limited by law to charitable purposes for the depreciable life of the equipment. Please note that for many non- U.S. entities, U.S. tax law considerations may affect whether the Bill & Melinda Gates Foundation will permit purchase of equipment with a depreciable life that is greater than the grant period being requested. In such cases, leasing would be preferable. The Bill & Melinda Gates Foundation provide limited indirect costs in accordance with its policy. Prior to submitting an LOI, please review the foundation's indirect cost policy at http://www.gatesfoundation.org/grantseeker/Documents/Indirect_Cost_Policy.pdf.

Travel funds are required to participate in one RFP-related meeting per year for up to 4 key members of the project team. Meetings will possibly be held at an international venue. Proposal budgets should factor in these costs.

E. Privacy

To help the Bill & Melinda Gates Foundation staff in their evaluation and analysis of projects, all proposals, documents, communications, and associated materials submitted to the Bill & Melinda Gates Foundation (collectively, "Submission Materials") will become the property of the Bill & Melinda Gates Foundation and may be subject to confidential external review by independent subject matter experts and potential co-funders in addition to analysis by the Bill & Melinda Gates Foundation staff. Please carefully consider the information included in the Submission Materials. If you have any doubts about the wisdom of disclosure of confidential or proprietary information, the Bill & Melinda Gates Foundation recommends you consult with your legal counsel and take any steps you deem necessary to protect your intellectual property. You may wish to consider whether such information is critical for evaluating the submission or if more general, non-confidential information may be adequate as an alternative for these purposes.

We respect confidential information we receive. Nonetheless, notwithstanding your characterization of any information as being confidential, the Bill & Melinda Gates Foundation may publicly disclose all

information contained in Submission Materials to the extent as may be required by law and as is necessary for potential co-funders and external reviewers, such as government entities, to evaluate them and the manner and scope of potential funding consistent with appropriate regulations and their internal guidelines and policies.

F. Warranty

By providing any Submission Materials, the sender warrants the Bill & Melinda Gates Foundation that they have the right to provide the information submitted. Applicants with questions concerning the contents of their Submission Materials may contact the Bill & Melinda Gates Foundation at: HIVDiagnostics@gatesfoundation.org.

G. Intellectual Property

Since the output of this program may lead to innovative technologies and/or products that will result in improved diagnostics for those that need them most in the developing world, the successful development of these high priority products may require substantial involvement and support of private sector industries as sub-contractors, and may also involve collaborations with multiple organizations, including academic and/or non-profit research institutions. It is the intent of this program to support the formation of appropriate public-private partnerships that are essential to meet these urgent global health needs. Intellectual property (IP) rights and the management of IP rights are likely to play an important role in achieving the goals of this program. To this end, the foundation requires that, even at the LOI stage, all applicants seriously consider their willingness to submit a full proposal in compliance with the foundation's proposal guidelines, a portion of which asks for certain information and intentions regarding intellectual property and global access concerns. Specifically, the Bill & Melinda Gates Foundation requires that you agree to use good faith efforts to conduct and manage the research, technologies, information and innovations involved in the Project in a manner that enables (i) the knowledge gained during the Project to be promptly and broadly disseminated, and (ii) the intended product(s) to be made available and accessible at reasonable cost to the developing countries of the world. The foundation refers to this as "Global Access." As part of the foundation's review and evaluation of each full proposal, due diligence will be conducted with respect to each participant's ability and commitment to manage intellectual property in a manner consistent with the stated scientific and charitable goals of the Bill & Melinda Gates Foundation. Due diligence activities may include inquiry into an applicant's:

1) Freedom to operate (FTO) and ability to freely use and acquire needed background technology;
2) Commitment to promote the utilization, commercialization and availability of inventions for public benefit in developing countries

In order to facilitate this due diligence process, applicants are encouraged to provide information with respect to the items above in their submission materials.

Applicants are also expected to make new information and materials known to the research and medical communities in a timely manner through publications, web announcements, progress reports to the foundation, and other appropriate mechanisms. These concepts may be discussed at some length with the applicants invited to submit full proposals, and will be addressed (to the extent appropriate) within each final grant agreement. The Global Access Strategy will also include provisions defining these concepts.

Research Assurances

While not necessary for the LOI, as applicable to the individual project, the Bill & Melinda Gates Foundation will require that for each venue in which any part of the project is conducted (either by your organization or a subgrantee or subcontractor) all legal and regulatory approvals for the activities being conducted will be obtained in advance of commencing the regulated activity. The foundation will further require you to agree that no funds will be expended to enroll human subjects until the necessary regulatory and ethical bodies' approvals are obtained.

A. Data Access Principles

In accordance with its charitable mission, the foundation is committed to optimizing the use of health-related data to translate knowledge into life-saving interventions. To this end, it is essential that data are made widely and rapidly available to the broader global health community through good data access practices.

Data access is intended to promote:

- *Innovation*, by encouraging diversity of analysis and opinion, facilitating evaluation of alternative hypotheses, permitting meta-analysis, and facilitating synthesis of results from individual projects into a larger whole, thereby promoting potentially lifesaving new insights.
- *Collaboration*, between teams and institutions, and among diverse disciplines, resulting in greater productivity and creativity.
- *Efficiency*, by preventing unnecessary duplication of effort, enabling secondary analyses of existing data, and enabling the redirection of resources to the most promising research endeavors, thereby maximizing the potential impact of investments.
- *Accountability*, by encouraging independent verification and analysis, thereby improving data quality
- *Capacity Strengthening,* by facilitating the education of new researchers and evaluators and enabling broader access to data for secondary analysis, which is of particular importance to investigators in developing countries.

B. Research Involving Human Subjects.

You agree that no funds will be expended to enroll human subjects in any research project subject to Institution Review Board (IRB) or independent ethics committee (IEC) approval until such approval has been obtained for each site.

C. Clinical Trials

We do not expect development or qualification projects in this program to require clinical trials on human subjects; in the unlikely situation that you do, a condition of this grant is your agreement that the appropriate Institutional Review Boards ("IRBs") and ethical committees will review and approve the clinical protocols prior to trial initiation. You further agree to conduct clinical trials associated with the project under the generally accepted principles of "Good Clinical Practices" as defined by the International Conference on Harmonization (ICH) E-6 Standard, the United States Food and Drug Administration (FDA), or the European Agency for the Evaluation of Medicinal Products (EMEA), as applicable. You acknowledge and agree that, as between you and the foundation, you take and will have full responsibility for all compliance, data safety, monitoring, and audit requirements of the relevant regulatory agencies, both for yourself and all other sites included in the project, including those activities conducted through sub-grants, subcontracts, or other collaborative efforts. You acknowledge and agree that any activities by the foundation as the grantor funding the Project, including its review of the Proposal or suggested modifications to the Project, does not modify the provisions of this paragraph or constitute the basis for any claim by you against the foundation.

D. Coverage for all Sites

You agree that for each venue in which any part of the Project is conducted (either by your organization or a subgrantee or subcontractor) all legal and regulatory approvals for the activities being conducted will be obtained in advance of commencing the regulated activity. You further specifically agree that no funds will be expended to enroll human subjects until the necessary regulatory and ethical bodies' approvals are obtained.

E. Regulated Activities

The coverage requirements set forth in the preceding paragraph include but are not limited to regulations relating to: research involving human subjects; clinical trials, including management of data confidentiality; research involving animals; research using substances or organisms classified as Select Agents by the U.S. Government; use or release of genetically modified organisms; research use of recombinant DNA; and/or use of any organism, substance or material considered to be a biohazard, including adherence to all applicable standards for transport of specimens, both locally and internationally, as appropriate. As applicable, regulated activities and their documentation are to be conducted under the applicable international, national, and local standards. Documentation of research

results should be consistent with regulations and the need to establish corroborated dates of invention and reduction to practice with respect to inventions where this is relevant.

F. Institutional Review Board (IRB) Approval

You agree to obtain the review and approval of all final protocols by the appropriate IRBs and ethical committees prior to enrollment of the first human subject and when using human material. A similar provision applies to Institutional Animal Care and Use Committee approval of studies involving animals, and Institutional Biosafety Committee for biohazards and recombinant DNA. You agree to provide prompt notice to the foundation if the facts and circumstances change regarding the approval status of the IRBs or ethical committees for any final protocol(s).

G. Provision of Care for Human Subjects Research

In keeping with "Good Clinical Practice" standards, you will disclose to subjects and the IRBs what care and/or referrals will be available through participation in the study. Institutional policies regarding what care will be provided to personnel who are injured as a result of their work on the Project should similarly be developed, approved and implemented with notice to the employees.

H. Use of Animals in Research

You agree to be responsible for the humane care and treatment of animals in projects supported in part or whole by foundation funds; and to adhere to the official guidelines for animal research applicable in the country and locality where the trial is being conducted. No grant funds may be expended on studies involving animals until all requisite approvals are in place, and notification to that effect has been provided to the foundation. For purposes of this provision, an "animal" is defined as any live, vertebrate animal used or intended for use in research, research training, experimentation, biological testing or for related purposes. In the case of multi-national collaborations, the standards of each country may be followed, as long as (i) differences do not interfere with the design and analysis of the Project, and (ii) regulations in your institution and host country do not conflict with the management of the Project.

You agree to take responsibility for compliance of all subgrantees or subcontractors (if any) with the appropriate animal welfare laws, rules and regulations. You must report annually as a part of your progress report that the activities are being conducted in accordance with applicable laws in each respective venue (e.g., U.S. grantees must use the U.S. Public Health Service standards. Non-U.S. grantees may cite national laws or the CIOMS International Guiding Principles for Biomedical Research Involving Animals (see http://www.cioms.ch/publications/guidelines/1985_texts_of_guidelines.htm) if there is not a relevant national standard.