Report Number : ICRR0020311

## 1. Project Data

| | |
|---|---|
| Project ID<br>P119051 | Project Name<br>Support to IAVI-Sendai Vector |
| Country<br>World | Practice Area(Lead)<br>Health, Nutrition & Population |

| L/C/TF Number(s) | Closing Date (Original) | Total Project Cost (USD) |
|---|---|---|
| TF-97822 | 30-Jun-2015 | 10,000,000.00 |
| **Bank Approval Date** | **Closing Date (Actual)** | |
| 24-Jun-2010 | 31-Dec-2015 | |

| | IBRD/IDA (USD) | Grants (USD) |
|---|---|---|
| Original Commitment | 9,260,256.00 | 9,260,256.00 |
| Revised Commitment | 9,260,256.00 | 9,260,256.00 |
| Actual | 9,260,256.00 | 9,260,256.00 |

Sector(s)
Health(100%)

Theme(s)
HIV/AIDS(100%)

| Prepared by | Reviewed by | ICR Review Coordinator | Group |
|---|---|---|---|
| Judyth L. Twigg | Soniya Carvalho | Joy Behrens | IEGHC (Unit 2) |

## 2. Project Objectives and Components

a. Objectives

According to the Grant Agreement (p. 3), the project's objective was "to support the International AIDS Vaccine Initiative (IAVI) in the development of a novel vaccine candidate that is based on the Sendai virus Vector, as a Global Public Good through a program of transitional research, product development and clinical trials."

At appraisal, Sendai virus was one of three paramyxoviruses under development in IAVI's novel vaccine vector portfolio, two of which were in the early design stage. It demonstrated unique properties with potential for eliciting a durable and highly targeted immune response in mucosal tissues where HIV initially amplifies and spreads. Sendai virus was IAVI's leading candidate and the most advanced in its readiness for evaluation in humans.

b. Were the project objectives/key associated outcome targets revised during implementation?

No

c. Components

The project contained two components:
1. Bank-executed Trust Fund activities (appraisal, US$ 0.54 million; actual, US$ 0.54 million). This component was to supervise the grant for the research program of development and trial of a novel HIV vaccine(s) based on Sendai virus Vector (SeV), including independent evaluations of the work. It was also to support administration of the Trust Fund, including monitoring of the Trust Fund, internal and external Trust Fund reporting, maintenance of the Trust Fund account, and ensuring compliance with audit requirements.

2. Recipient-executed Trust Fund activities (appraisal, US$ 9.26 million; actual, US$ 9.26 million). This component was to develop and conduct clinical trials of HIV vaccine candidates based on SeV: virulence and preclinical safety studies, manufacturing, and the first phase of clinical trials (regulatory, ethical, and biosafety clearances), through: (a) construction of vaccine candidates using SeV as a vector encoding different HIV genes, or antigens; (b) conducting of virulence and preclinical safety studies in animals with the newly constructed candidates for suitability for advancement into clinical trials in humans; (c) development of manufacturing processes for the production of vaccine material at a scale and standard suitable for clinical trial; and (d) conducting of the first stage of clinical trials (Phase I) of the SeV-based HIV vaccine candidates in humans, alone as well as coupled in a prime-boost regimen, to assess vaccine safety, elicited immune responses, and "proof of concept" studies. Clinical trials were initially expected to take place in the United States and United Kingdom (PAD, p. 32), but eventually were conducted in the United Kingdom, Kenya, and Rwanda.

d. Comments on Project Cost, Financing, Borrower Contribution, and Dates

Project Cost, Financing, and Borrower Contribution: The project was designed as a free-standing single-donor Recipient Executed Trust Fund (RETF) in the amount of US$ 10 million, financed by the Japan Ministry of Finance. The entire amount was disbursed. The United States Agency for International Development (USAID), as well as other unspecified donors, contributed other financing to the research effort, with the Bank supporting mostly the upstream non-clinical work and USAID contributing mostly to clinical development. The contributions from all donors, including the Bank, totaled US$ 20.15 million.

Dates: The project was approved on September 15, 2010 and became effective on March 8, 2011. The mid-term review took place as scheduled, in June 2013. The planned work program was five years. A level-2 restructuring on April 28, 2015 extended the closing date by six months, from June 30, 2015 to December 31, 2015, and added one outcome indicator. This restructuring was in response to delays in the construction of second-generation vaccine candidates and a consequent shift from a staggered to a more sequential approach between the first- and second-generation candidates, waiting for clinical trial results before launching preclinical and manufacturing activities, and eventually the conducting of an additional non-human primate study that had not been originally planned to compare replication-competent vectors (SeV-based and vesicular stomatitis virus-based).

## 3. Relevance of Objectives & Design

a. Relevance of Objectives

When the operation was initially prepared, the AIDS epidemic continued to impact health, food security, education, poverty, and stability world-wide, with 7,400 people newly infected and 5,500 people dying of AIDS daily in 2008. A preventive vaccine was seen as one of the primary hopes for decelerating and ultimately ending the epidemic. Analysis conducted by IAVI showed that a vaccine that is 50% effective and reaches 30% of the targeted population could avert 5.7 million new infections over a fifteen-year period. The project's objectives were therefore highly relevant to global conditions at the time of appraisal. They remain highly relevant at project closing due to the continued need for an HIV vaccine and the overall slow progress of the global HIV vaccine pipeline. The objectives are also highly relevant to the World Bank Group's corporate goals of ending extreme poverty and promoting shared prosperity, both of which are tied to curbing and ending the AIDS pandemic, and to achievement of the Sustainable Development Goal of ensuring healthy lives and promoting well-being for all at all ages.

Rating
High

b. Relevance of Design

There was a logical and plausible link between the project's planned activities and its expected outcomes. The project's development plan, including parallel work on second-generation candidates, is standard in the pharmaceutical industry. IAVI's institutional arrangements were solid in terms of scientific, technical, project, and financial management capacity.

Rating
High

## 4. Achievement of Objectives (Efficacy)

### Objective 1

Objective
Support the International AIDS Vaccine Initiative (IAVI) in the development of a novel vaccine candidate that is based on the Sendai virus Vector

Rationale
Outputs:
Three different vaccine candidates were constructed, including genetic stability assessments. Virulence and pre-clinical safety studies were conducted in animals with two of the three newly-constructed candidates (SeV-Gag and SeV-HIV-Immunogens) to assure that they would be suitable for advancement into clinical trials with humans. The full preclinical package (virulence, immunogenicity, toxicity studies) was constituted for SeV-Gag, and immunogenicity studies were conducted for two other constructs. A total of 16 approvals from regulatory authorities and ethics committees were obtained. A manufacturing process for large-scale production of clinical trial material for SeV-Gag was developed; the manufacturing processes for the other two candidates were put on hold pending additional results. A Phase I clinical trial was conducted in humans to assess SeV-Gag vaccine safety as well as immune responses, including a one-year follow-up post last vaccination in the last quarter of 2015. Clinical sites were located in the United Kingdom, Rwanda, and Kenya (although the PAD states that the Phase I trials were to take place in the United States and United Kingdom, the project team later confirmed that it has long been IAVI practice to build local capacity to conduct health research (including clinical trials and vaccine development) in African countries; this possibility was noted in the PAD, p. 20).

Outcomes:
Although the Phase I trial for SeV-Gag fully met its objectives in regard to implementation, completion, and analysis, the immunogenicity results did not pass the pre-selected criteria to pursue the development of second-generation vaccine candidates. However, these results did not negate the viability of SeV as a vector for HIV vaccines, and these results confirmed that the combination of a replicating vector and intranasal administration was a promising approach. Pharmaceutical development (manufacturing and preclinical studies) of a second-generation candidate has not gone forward as initially planned, but IAVI is leveraging a planned non-human primate study to include one of the second-generation candidates (SeV-EnvF). The project successfully generated knowledge about replication-competent vectors that is being translated to other promising vaccine candidates.

Rating
High

## 5. Efficiency

Neither the PAD nor the ICR provide traditional economic analysis, as the usual metrics are difficult to apply. Although the project was completed within its original budget envelope and largely on time (only one six-month, no-cost extension), there was some deviation from the originally planned operating costs (in particular, the contractor costs for vector construction escalated from US$ 0.5 million to US$ 2.5 million). The total US$ 20 million budget for bringing a candidate vaccine with a proof-of-concept in animals to completion of a phase I trial, including work on second-generation candidates, is high compared to industry benchmarks, but is explained by two factors: limited competition between service providers, as few contract research and manufacturing organizations have the capacity to handle this type of vaccines; and the extensive phase I trial in three different countries, with a novel route of administration and the need to build capacity in Rwanda and Kenya (ICR, p. 11). The capacity development in African countries is standard practice for IAVI and an important positive externality of the project.

Delays emerged at several points:

- At the initiation of the SeV clinical trial, results were published by an investigating team for another, unrelated HIV vaccine candidate that raised safety concerns. Out of an abundance of caution, IAVI put volunteer enrollment on hold until appropriate discussions were held with regulatory authorities and the informed consent document was updated, causing a delay of 41 days (ICR, p. 6).
- Legal and administrative issues caused a two-year delay in the construction of second-generation vaccine candidates, as the candidate eventually pursued was not the one originally planned. Delays centered around filing the provisional patent on the new gene sequences designed by IAVI prior to transferring those sequences to the Japanese partner responsible for constructing the corresponding vectors, and then receiving required clearance from the Japanese Ministry of Education, Culture, Sports, Science and Technology in compliance with national biosafety regulations.

As explained by the project team, the shift to a second-generation vaccine candidate different from the one originally planned entailed some additional costs and delays; however, this is the nature of the scientific research process. The decision to pursue a different candidate constituted a cost-effective use of resources. In the end, the project closed with only a six-month extension, and clinical trials are ongoing as planned (project benefits were as originally anticipated).

Efficiency Rating
Substantial

a. If available, enter the Economic Rate of Return (ERR) and/or Financial Rate of Return (FRR) at appraisal and the re-estimated value at evaluation:

| | Rate Available? | Point value (%) | *Coverage/Scope (%) |
|---|---|---|---|
| Appraisal | | 0 | 0<br>☐Not Applicable |
| ICR Estimate | | 0 | 0<br>☐Not Applicable |

* Refers to percent of total project cost for which ERR/FRR was calculated.

## 6. Outcome

Relevance of the project's objectives and design is rated High, as the project responded to urgent global needs and within the framework of World Bank corporate strategy, and its development plan linked planned activities logically and plausibly to expected outcomes. Achievement of

the objective to support IAVI in the development of a novel vaccine candidate based on SeV is rated High, with all expected benchmarks met, phase I clinical trials conducted, and results harnessed for further study. Project efficiency is rated Substantial, as the project directed funds toward promising vaccine candidates according to high-level technical criteria and guidance. Taken together, these ratings are indicative of no shortcomings in the project's preparation and implementation, and therefore an Outcome rating of Highly Satisfactory.

a. Outcome Rating
Highly Satisfactory

## 7. Rationale for Risk to Development Outcome Rating

Work performed on this project has significantly advanced IAVI's viral engineering, vector design, and molecular virology expertise and capacity, as well as strengthening its ties with other key stakeholders in the field of replication-competent vectors. The final non-human primate study financed by the project is continuing (backed by the Bill and Melinda Gates Foundation), with efficacy data expected by the end of 2017. Regulatory authorities in both developed and developing countries have developed capacity to handle new products. The significant capacity for conducting clinical trials of a vaccine delivered via the intranasal route that was developed in Kenya and Rwanda is likely to be sustained.

As the ICR (p. 12) notes, there is obviously a significant risk that no SeV-based vaccine will ever successfully complete clinical development and be approved, but that was not this project's objective. The project's achievements -- investigation of the viability of SeV as a vector for HIV vaccines, pointing out appropriate directions to carry forward the replication-competent vector platform -- are unlikely to be reversed. Furthermore, the project team added that the Government of Japan has committed US$ 2 million for follow-on research, with an additional commitment likely to be forthcoming.

a. Risk to Development Outcome Rating
Negligible

## 8. Assessment of Bank Performance

a. Quality-at-Entry

The project proposal underwent a thorough technical quality and feasibility review by two highly qualified scientists who judged the quality of the proposal to be sound, clearly developed, and modestly costed. Full financial management and procurement assessments concluded that IAVI's capacity was adequate to meet Bank requirements. The project team conducted a thorough risk assessment, with high risk assigned to the possibility that the eventual product would not be an effective HIV vaccine and to the inherent risks associated with clinical trials in human subjects, and substantial risk to financing because of the trust fund-dependence of the work. Overall risk was assessed as high because of the innovative nature of the work being attempted. The risk was to be mitigated by managing expectations and making it clear that, even if a viable vaccine were not produced, the fundamental research being supported would contribute substantially to knowledge in the field, and also by conducting the clinical trials in the United States, with the usual approvals and safeguards stipulated by the US Food and Drug Administration (and those same standards applied to any trials conducted elsewhere). The project's results framework was comprehensive and clearly specified, with activities carefully sequenced and linked to a set of well constructed performance indicators. However, as the ICR (p. 14) notes, some foreseeable implementation risk, related to legal and administrative issues, was understated (and some of this risk eventually materialized; see Section 5).

Quality-at-Entry Rating
Satisfactory

b. Quality of supervision

The ICR identifies no shortcomings in Bank supervision. Regular missions took place at IAVI headquarters to review progress, and the Task Team Leader visited the clinical research sites in the United Kingdom, Kenya, and Rwanda. The Bank and IAVI maintained a collaborative relationship, particularly with regard to fiduciary management and safeguards issues. The mid-term review was conducted on time by two independent experts with research & development and private sector experience. The team, with high-level technical oversight from the World

Health Organization and the U.S. National Institutes of Health, made the scientifically sound and cost-effective decision to pursue an alternate second-generation candidate, effectively managing the legal and administrative risks noted in Section 8a. Appropriate revisions were made to the results framework in a timely manner.

Quality of Supervision Rating
Highly Satisfactory

Overall Bank Performance Rating
Satisfactory

## 9. Assessment of Borrower Performance

a. Government Performance
Not applicable.

Government Performance Rating
Not Rated

b. Implementing Agency Performance
IAVI was the primary implementing agency of the project. It either directly executed or oversaw all activities related to the development and clinical trials of HIV vaccine candidates based on SeV. It also selected and managed the contract organizations responsible for specific activities like preclinical studies and drug product manufacturing. Where IAVI had a comparative advantage, it carried out activities internally, including clinical development (appropriate given IAVI's long-standing relationships with specific clinical research centers, the intent to develop African leadership and ownership of HIV vaccine research, and its competitive clinical research costs). Some procurement issues occurred early in the project period due to IAVI's misunderstanding of prior review commitments, but these questions were promptly and easily resolved. There were no issues with safeguards or fiduciary compliance.

Implementing Agency Performance Rating
Satisfactory

Overall Borrower Performance Rating
Satisfactory

## 10. M&E Design, Implementation, & Utilization

a. M&E Design
IAVI was to monitor and evaluate the progress of the project and prepare reports on the basis of a set of 26 carefully sequenced indicators across five sequential sub-objectives: constructing vaccine candidates; conducting virulence and pre-clinical safety studies in animals; obtaining approval from ethical and regulatory bodies; developing manufacturing processes for large-scale production of clinical trial material; and conducting the Phase I clinical trial in humans. IAVI was also to participate in annual technical briefings to the Donor in Tokyo, at which progress was to be presented by IAVI and its consultants and contractors.

b. M&E Implementation
The results framework was used regularly to monitor progress. During implementation, IAVI requested minor adjustments to the framework to accommodate changes to the development plan, including the addition of one outcome indicator and removal of irrelevant intermediate results

indicators as the strategy for the second-generation vaccine candidates changed.

c. M&E Utilization

Results were consistently used throughout implementation to determine whether and how to move to the next planned phase of the operation.

M&E Quality Rating

High

## 11. Other Issues

a. Safeguards

The project was environmental category "B" and triggered OP/BP 4.01, Environmental Assessment. Several Bank safeguards specialists reviewed IAVI's project proposal and concluded that it appeared scientifically sound. The safeguards review covered issues related to social safeguards (Institutional Review Boards and Ethics Committees, informed consent, community advisory boards, privacy personal information disclosures) and environmental safeguards (biosafety measures during vaccine construction, studies, manufacturing, testing, waste management). A Social Impact Supervision Plan was specified. Mitigation of environmental risk included engagement of an accredited/certified Contract Research Organization laboratory in Japan for vaccine construction and studies, an accredited/certified Contract Manufacturing Organization in Japan for manufacture of prototype vaccine, and certified healthcare institutions in the United States for Phase I clinical trial and assay development. All research, analytical, manufacturing, and healthcare institutions were to be subject to a due diligence review by the Bank for environmental safeguards purposes. During implementation, all Institutional Review Boards and Ethics Committees were appropriately engaged in the United Kingdom, Rwanda, and Kenya. Clinical safety during the trial was monitored by an internal Protocol Safety Review Team and an external independent Safety Review Board. The ICR (p. 7) states that no safeguards issues arose during implementation and that there was compliance with the Bank's safeguards policies.

b. Fiduciary Compliance

Procurement and financial management were well handled throughout the project, and according to the ICR (p. 8), there was compliance with the Bank's fiduciary policies. IAVI's Audit & Finance Committee ensured the integrity and reliability of financial reporting, risk management, and verification and oversight of whistleblower reports. There was one issue at the beginning of the project due to a misunderstanding of the Bank's prior review procedures; IAVI made substantial amendments to contracts after receiving an initial non-objection and without submitting those changes for prior review, necessitating a retroactive non-objection. IAVI adjusted its procedures for all subsequent procurement processes.

c. Unintended impacts (Positive or Negative)

None reported.

d. Other

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## 12. Ratings

| Ratings | ICR | IEG | Reason for Disagreements/Comment |
|---|---|---|---|
| Outcome | Highly Satisfactory | Highly Satisfactory | --- |
| Risk to Development Outcome | Negligible | Negligible | --- |
| Bank Performance | Highly Satisfactory | Satisfactory | Some implementation risks (legal and administrative issues) were understated at preparation. According to OPCS/IEG harmonized guidelines, when one sub-rating under Bank Performance is Highly Satisfactory and the other Satisfactory (as is the case in both the ICR and this ICR Review), the overall Bank Performance rating is Satisfactory. |
| Borrower Performance | Satisfactory | Satisfactory | --- |
| Quality of ICR | | Substantial | --- |

Note
When insufficient information is provided by the Bank for IEG to arrive at a clear rating, IEG will downgrade the relevant ratings as warranted beginning July 1, 2006.
The "Reason for Disagreement/Comments" column could cross-reference other sections of the ICR Review, as appropriate.

## 13. Lessons

The ICR (pp. 16-19) offers several in-depth and insightful lessons, including:
As the Bank launches the Pandemic Emergency Financing Facility, there are important lessons to be learned from its earlier experience in financing vaccine, antiviral, and antibiotics research. As that experience is relatively limited, in this case the mature and comprehensive technical expertise of the grantee (IAVI) was key.
Openness and flexibility help manage events in an environment that is almost always unpredictable. In this case, close collaboration and communication helped the team to deal with situations involving identification of new sites for clinical trials and emergence of unanticipated results from a similar immunization approach as clinical trials were being initiated.

## 14. Assessment Recommended?

No

## 15. Comments on Quality of ICR

The ICR is clear, concise, and evidence-based. It efficiently describes implementation experience and underscores the novel challenges and ambitions of the project, with sufficient explanation of technical details for a lay reader to understand its achievements. The ICR's lessons are particularly insightful, though they introduce a considerable amount of new information that might usefully have been included earlier in the document.

a. Quality of ICR Rating

Substantial