1. PUBLISHABLE SUMMARY

Summary of the context and overall objectives of the project (For the final period, include the conclusions of the action)

The European HIV Vaccine Alliance (EHVA) program has as major goal to develop a Multidisciplinary Vaccine Platform (MVP) in the fields of prophylactic and therapeutic HIV vaccines. The Specific Objectives are to build up:
1) Discovery Platform. The overarching Goal is the generation of novel vaccine candidates in the field of prophylactic and therapeutic vaccines inducing potent neutralizing and non-neutralizing antibody responses and T-cell responses (for therapeutic vaccines); the specific Objectives of the Discovery Platform to achieve this goal are: a) improvement of Env protein-based vaccine immunogenicity, b) improvement of vaccine regimens, i.e. prime/boost combinations, and c) transient break of immunological tolerance.

2) Immune Profiling Platform. The primary Goal is to rank novel and existing (benchmark) vaccine candidates in pre-clinical and human clinical trials; the ranking will be performed through the use of a large set of validated, qualified and standardized immunological assays and the access to the most advanced technologies in the profiling of the immune responses.

3) Data Management/Integration/Down-Selection Platform. The primary Goal is to provide powerful statistical tools for the analysis and interpretation of complex data and algorithms for the efficient selection of vaccine candidates at the different stages, i.e. pre-clinical and clinical, of vaccine development.

4) Clinical Trials Platform. The primary Goal is the acceleration of clinical development of novel vaccine candidates and the early prediction of failure of vaccine candidates. This will be achieved through innovative design in clinical trials such as Experimental Medicine Trials and Adaptive Design and allow identification of improved vaccine regimens in the prophylactic setting and of immune correlates of protection in the therapeutic setting.

Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far (For the final period please include an overview of the results and their exploitation and dissemination)

In the second period, significant progress has been made towards EHVA's four overarching objectives:

1) Discovery Platform. The main effort is focused on the down-selection of novel Env protein based, RNA-based and VSV vector based vaccine candidates.
a. Novel Env protein based vaccine candidates: In Year 1 EHVA has successfully generated a number new candidates that are based on: 1) glycan shielded gp120 monomeric glycoprotein CoreE to focus B cells on the CD4bS and the 322 glycan supersite; 2) improved SOSIP-like Env trimers with structure-based mutagenesis to introduce stabilizing residues; 3) improved SOSIP-like Env trimers with structure-based chemical crosslinking approaches.
In the second period, continued efforts have been made on further improvement of these candidates and on extensive biochemical and biophysical characterization. The lead candidates have been evaluated in a number of in vivo small animal immunogenicity studies, and the plan is to move the best-in-class of these candidates to NHP study.

b. RNA-based vaccine candidate: Based on the non-human primate data, DREP has been selected for clinical development.
c. VSV vector: significant effort has been made to further improve the VSV based candidates both from a vector and an antigen perspective, which resulted in a panel of new recombinants. In parallel, a number of mouse immunogenicity studies have been conducted to evaluate homologous and heterologous prime-boost regimens combining VSV with NYVAC, DNA and protein and have demonstrated that VSV is highly immunogenic both in terms of T-cell and antibody responses.

2) Immune Profiling Platform. Continued efforts have been made on the validation of novel assays to assess innate and adaptive immune responses and in preparation for the first therapeutic trial (EHVA-T01). This includes but not limited to: 1) validation of multiparameter flow cytometry, multiplex technology and CyTOF for innate and adaptive immunity; 2) validation of the neutralizing antibody assay; 3) standardization of CD8 T cell virus inhibition assay..

3) Data Management/Integration/Down-Selection Platform. Main effort is focused on: 1) building the EHVA Data Warehouse based on the LabKey software; 2) introducing Data Analytical Platform based on SHINY framework; 3) developed new algorithm for the automatic gating of cells using flow cytometry data.

4) Clinical Trials Platform. With the endorsement of the SAB on the redesign of the therapeutic trial (EHVA-T-1) to incorporate vedolizumab, the main effort is focused on the development of the protocol and other study related documents, as well as the ethics and regulatory approval in six European countries. At the time of this report, approval has been obtained in UK and Switzerland, and the target start date of the trial is Q3 2018. EHVA-T-1 is the first trial evaluating the combination of therapeutic vaccines with vedolizumab, with an innovative Multi-Arm-Multi-Stage trial design.

Progress beyond the state of the art, expected results until the end of the project and potential impacts (including the socio-economic impact and the wider societal implications of the project so far)

EHVA program will lead to a number of innovation potentials:
• Large portfolio of vaccine candidates: EHVA aims to develop multiple vaccine approaches, including novel Env protein, RNA, replication competent vector, novel delivery system and adjuvants. Combination of these strategies increases the chance of a successful novel candidates. Innovation management combined with the robust screening platform (see below) will at the same time ensure early termination of less promising candidates and prioritizing to move the most promising candidate forward.
• Robust screening platform for early selection of vaccine candidates/regimens: Currently, more than 20 HIV candidate vaccines are in early clinical development, and the number of potential immunization strategies is much larger taking into consideration of the possible prime-boost combinations, number of injection and injection intervals. Efficient screening and early selection of the most promising candidate/regimen has been a challenge. The robust immunological and data integration platform of EHVA represents a strong tool to address this challenge not just for the HIV field but can be applied to other fields as well.
• Innovative clinical platform for the evaluation of vaccine candidates: EHVA promotes the Experimental Medicine and Adaptive Trial concept in the design of its trials. Combined with the comprehensive immunological profiling algorithm performed by centralized core labs with standardized/validated assays and centralized analysis with high dimensional data integration, these

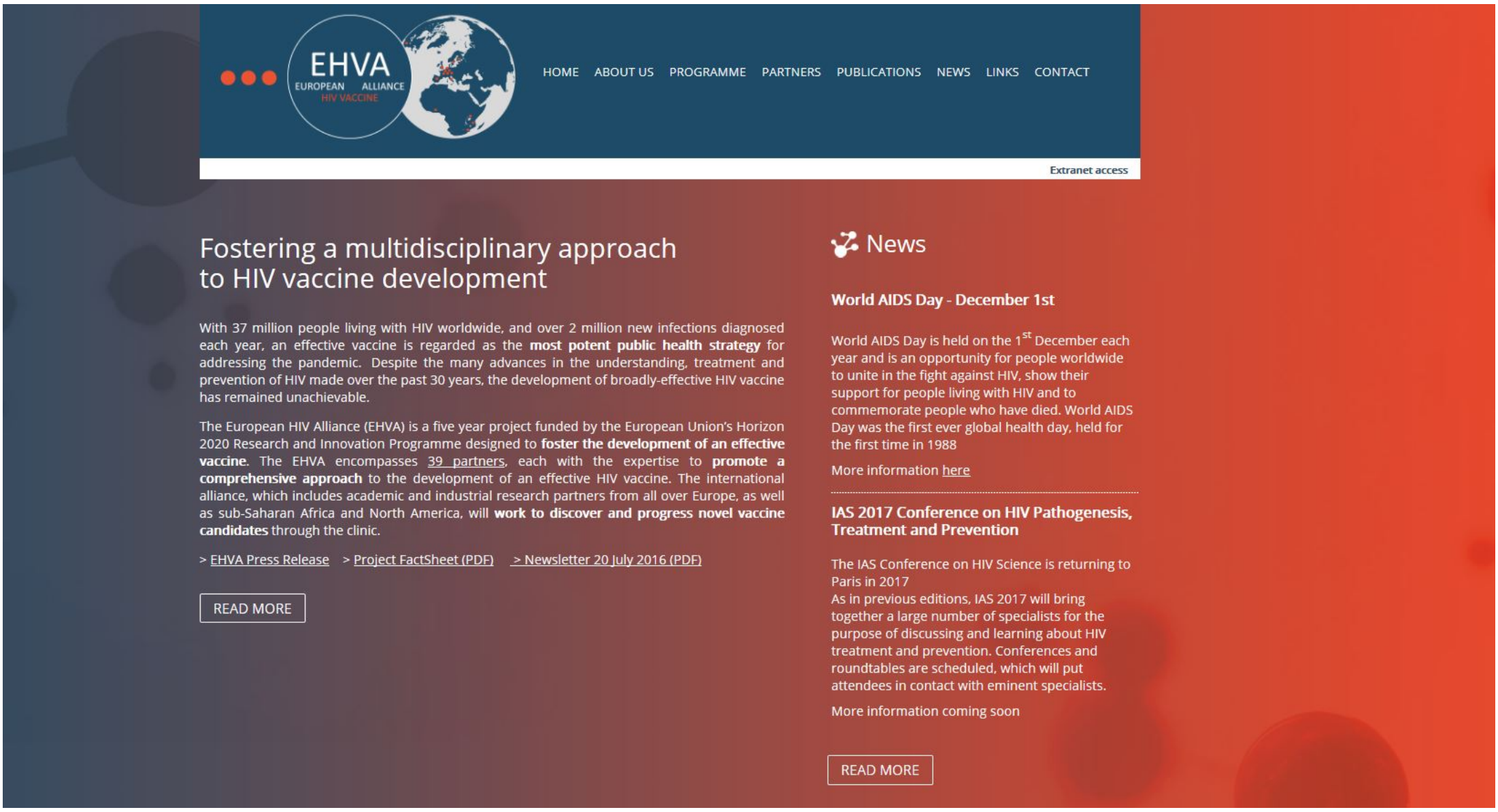
innovative designs will allow rapid evaluation and selection of the best-in-class vaccine candidates. Again such platform can be applied for the evaluation of other HIV or non-HIV vaccine candidates.

In summary, the powerful and highly innovative immunological, clinical and data integration platforms developed under EHVA will contribute to expediting the selection and development of promising vaccine candidates. This centralized and standardized pool of knowledge will enable new and less risky solutions for all public/private partnerships striving to develop HIV vaccines. The success of EHVA will contribute to reducing the cost of R&D programs, giving a higher visibility and credibility of the European research in the HIV vaccine field and be very adaptive to the evolution of the techniques and sciences. This will provide a basis for international standards that could be broader than HIV vaccines.

Address (URL) of the project's public website

http://www.ehv-a.eu/

EHVA website Homepage



WPs Per Chart