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AIDS Vaccine Integrated Project (AVIP):
A Novel Program and Developing Countries Partnership
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Vaccines based on viral structural products (Env/Gag/Pol) alone have failed to prevent infection by HIV/SIV. More recently, vaccines based on viral regulatory gene products (Tat/Rev/Nef) have been shown to contain virus replication and to prevent disease onset. A vaccine combining both regulatory and structural viral antigens (combined vaccine) is likely to be superior to the former since it induces immune responses to both early and late viral products. The mission of the AIDS Vaccine Integrated Project (AVIP) is to develop novel combined vaccines to be tested in phase I preventive and therapeutic trials in Europe, that are suitable for future testing in phase II/III trials in Developing Countries (DC), and to foster training, technology transfer and community involvement between EU and DC. To ensure completion of the program, priority has been given to vaccine combinations containing single antigens for which efficacy has been demonstrated in animal models and phase I studies have been completed or are ongoing.

Non-structural vaccine antigens have proven to be safe and immunogenic in preclinical and clinical trials. Promising efficacy data have also been obtained in nonhuman primates, where immunity to non-structural viral proteins contributed to protection against challenge with pathogenic SIV or SHIV strains. In particular, novel vaccine strategies combining non-structural and structural antigens have been developed with the aim of inducing broad cellular and humoral immune responses able to eliminate infected cells and to neutralize infectious virions, respectively [1]. The optimization of formulations and immunization schedules is particularly important, especially in view of the risk that structural, immunodominant viral products, such as Gag and Env, may diminish the response against small regulatory proteins. This potential complication was suggested by preclinical studies that included Gag, Env, Tat, Rev and...

Fig. 1: Vaccine development pipeline
<table>
<thead>
<tr>
<th>Combined vaccine candidates (clade)</th>
<th>Single components (clade)</th>
<th>Mouse safety and immunogenicity</th>
<th>Mouse efficacy</th>
<th>Monkey safety and immunogenicity</th>
<th>Monkey efficacy*</th>
<th>GMP development</th>
<th>Approval for human use</th>
<th>Clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. HIV Tat + ΔV2 Env (B, C)</td>
<td>HIV Tat (B)</td>
<td>D</td>
<td>ND</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>ongoing (pHIV- and HIV+).</td>
</tr>
<tr>
<td>2. HIV Nef + ΔV2 Env (B, C)</td>
<td>HIV ΔV2 Env (B)</td>
<td>D</td>
<td>ND</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>ongoing (pHIV)</td>
</tr>
<tr>
<td>3. Multi HIV vaccine antigens and epitopes 1</td>
<td>MVA, HIV Nef (B)</td>
<td>D</td>
<td>ND</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>completed (HIV+)</td>
</tr>
<tr>
<td></td>
<td>HIV ΔV2 Env (B)</td>
<td>D</td>
<td>ND</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>ongoing (HIV+)</td>
</tr>
<tr>
<td>4. HIV multigene [Nef, Rev, Tat (B) and Gag, RT, Env (A, B, C)]</td>
<td>GTU-MultiHIV B clade**</td>
<td>D</td>
<td>D</td>
<td>ND</td>
<td>ND</td>
<td>D</td>
<td>D</td>
<td>ongoing to be started (HIV- and HIV+)</td>
</tr>
<tr>
<td></td>
<td>HIV Nef, Rev, Tat (B)</td>
<td>D</td>
<td>D</td>
<td>ND</td>
<td>ND</td>
<td>D</td>
<td>D</td>
<td>completed (HIV- and HIV+)</td>
</tr>
<tr>
<td></td>
<td>HIV Gag, RT Env (A, B, C)</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>ongoing (HIV+)</td>
</tr>
</tbody>
</table>

1. Multi HIV A, B, C, or FGM clade antigens and epitopes = full length Rev, Env, Tat, nef, gag gag p17, p24 antigens full length and over antigens + 0 T cell antigens from Pol, Protease, Env antigens; 20 = Done; 0 = No Data; 4 HIV-P: prevention non-infected individuals; 5 HIV-T: therapeutic HIV-infected individuals. **MVI GTN is used for monkey efficacy studies. *Test generation vector.

Tab 1: Preclinical and clinical data of the vaccine candidates to be tested in phase I trials within the AVIP Project: previous work and development stage of single antigenic components

Nef and by the pattern of immune responses detected in the course of natural infections. At the same time, other studies indicate that HIV regulatory proteins (i.e., Tat and Nef) have key immunomodulatory properties, which can be exploited as part of antigen combinations. Therefore, the combination of regulatory and structural gene products requires a rational vaccine design, appropriate formulations of the antigens, and/or immunization protocols to ensure induction of balanced responses to all antigens. These strategies are currently under evaluation within AVIP, an EU Commission awarded integrated project (6th Framework Programme). In this program, several combinations of non-structural and structural gene products are being tested in preclinical studies to select the best candidates that will enter phase I preventive and therapeutic trials. The polyvalent vaccine approach is the most promising for both therapeutic and prophylactic efficacy, as indicated by preclinical studies. For this reason, AVIP strategy, useful for both preventive and therapeutic interventions, includes both nonstructural and structural viral products. In fact, the immune responses to the regulatory proteins Tat, Rev and Nef have been shown to play a significant role in controlling disease onset and progression. Further, with regard to Env, modifications (i.e., deletion of the V2 loop of Env ΔV2-Env) have been introduced by

partners of this consortium that permit exposure of epitopes that are conserved around the clade issue. Accordingly, four different vaccine candidates have been selected in AVIP and are:
- Tat + Env (V2-deleted)
- Nef + Env (V2-deleted)
- Multi-HIV antigens/epitopes [rev, tat, nef, gag p17, p24] full-length antigens, and over 20 T cell epitopes from Pol, Protease and Env antigens
- HIV multigene (nef, rev, tat, gag, rt, env)

The efficacy of the different antigens present in the AVIP vaccine candidates has been shown in animal models and these antigens have been or are being tested in humans (Table 1). Comparative analysis in both preclinical studies and phase I therapeutic and preventive trials of these vaccines will be key for the selection of vaccine candidates for phase II/III trials in DC. To this end, clinical sites have already been set up in Estonia, Finland, Germany, Italy, Sweden, and the United Kingdom. Partners involved in the clinical development have wide experience with regulatory issues, Good Manufacturing Practice (GMP) production, study design and site preparation, ethical issues, and Community Advisory Board (CAB) involvement. In addition, the support of the already established Program EVA Centralised Facility for AIDS Reagents (NIHSC, UK) with repository and distribution function is of key value to this project. This will constitute selected from a larger pool based on two criteria: the combination of HIV regulatory (Tat and/or Rev, and/or Nef) with structural (Env and/or Gag/Pol) genes/products, and the advanced stage of development of the single components, including efficacy studies in both monkeys and new murine models, GMP process development, and phase I studies. Training, education and technology transfer activities are also within the general scope of the program and are viewed as preparatory to advanced clinical trials with selected AVIP vaccine candidates that will eventually be performed in DC. Therefore, AVIP major objectives are:

1. To conduct parallel preventive and therapeutic phase I trials in Europe with four novel combined vaccines. The candidates will be first tested in preclinical models to optimize the formulations and the vaccination protocols.
2. To perform feasibility studies and technology transfer in DC for future phase II/III trials.
3. To carry out training in EU countries and DC. To this end, the AVIP International School has been established.
4. To ensure community involvement both in EU countries and DC to guarantee the correct ethical information of the volunteers, counselling, quality of life evaluation and risk assessment.

an optimal basis for the standardization of techniques and procedures, and for supporting all AVIP Research, Technological Development and Demonstration activities.

Objectives and Scientific Structure

The general aim of AVIP is to generate novel HIV-1 vaccine candidates to be tested in phase I preventive and therapeutic trials in Europe within a 5-year program (Fig. 1). To achieve this goal, 4 novel vaccines have been...
The AVIP project is managed through a Steering Committee (SC), which is the governing body of the AVIP. The SC is supported by the Advisory Board (AB) and the Monitoring Committee (MC), which oversee the scientific, technological, innovative, regulatory, clinical, and training related activities of the project, with particular regard to ethical and social issues including community involvement and gender issues.

Potential Impact

1. The combination of regulatory and structural genes to generate vaccines against HIV/AIDS will ensure an immune response to both early and late gene products, thereby stimulating a broad and potentially protective immune response. The advanced stage of development of the combined vaccine candidates will ensure completion of four therapeutic and four prophylactic phase I clinical trials within the program in the most cost-effective way.

2. Cooperation with DC is one of the main activities of AVIP. This collaboration constitutes the basis for building up the capacity in DC sites. The training and standardization of techniques and procedures, in both the clinical sites and core laboratories for performing phase I clinical trials in EU, will ensure the reproducibility of all results among the various sites, and the maintenance of the highest level of internal and external quality control. Of critical importance will be the establishment or expansion of CAB in the EU and with DC to ensure the ethical recruitment of volunteers, volunteers’ information, quality of life and risk assessment, and communication issues.

3. Training in a broader sense is also being pursued in all AVIP activities, both in the EU and in DC at both the levels of development and demonstration activities. The AVIP International School, which has been created by joining existing centers in the EU and South Africa, will be the main instrument for the training activity. As many of the assays and other aspects of the phase I trials will be used in future phase II and III trials in South Africa, the participation of South African researchers will promote continuity in the development of the vaccines.

4. The support of the already established Program EVA Centralised Facility for AIDS Reagents, which has repository and reagent distribution functions, gives added value to this project. It also constitutes an optimal basis for the harmonization and standardization of techniques and procedures, and for supporting all RTD and demonstration activities.

5. The AVIP consortium is exploiting synergies with national and international ongoing programs, including the following that are already existing: (i) National program in the participating countries, such as the Italian Concerted Action on HIV/AIDS Vaccine development (ICAV) and the Swedish International Development Cooperation Agency (SAREC/SIDA), and (ii) bilateral programs with DC (Italy-South Africa, Italy-Uganda, Italy-Swaziland, Sweden-Tanzania, UK-Uganda) and European programs, such as the HIV Incidence Study (HIVIS) and the Very Innovative AIDS Vaccine (VIVAN). In this respect, the AVIP consortium is also establishing interactions with International Organizations, so that cooperation with other EU and international networks and agencies is foreseen.

6. Scientific publications and communications at national and international meetings will constitute an additional forum for AVIP dissemination plans in the scientific and industrial community. Promotion of public awareness concerning the goals, activities and results of the AVIP consortium will be ensured by an internet web site (www.avip-eu.org), which is being developed for disseminating AVIP results and for internal consortium management.

The results of the AVIP program may lead to significant improvement of living conditions in both developing and developed countries. By increasing human life expectancy and health of the youth, the major work force of the countries affected by the HIV epidemic will be preserved, thereby reducing the tremendous social and economic loss due to AIDS.

Reference


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