

# Epidemiological and clinical usefulness of HIV/AIDS Cohort Studies: Towards a global collaboration

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Nowadays, combination Antiretroviral Therapy (cART) has led to shifting patterns of morbidities and mortality<sup>1-5</sup> with important consequences for clinical practice: 1) incidence of AIDS events has dramatically decreased and median time to AIDS may reach 20 to 30 years<sup>6</sup>, 2) complications of HIV/AIDS are now responsible for only a minority of causes of death<sup>5,7</sup>, 3) emerging causes of death and morbidity, i.e. cancers<sup>8,9</sup>, cardio-vascular diseases<sup>10,11</sup> and bacterial infections<sup>12</sup>, occur with especially high frequency or earlier than expected, as compared with the general population. In addition, available antiretroviral therapy is better tolerated, but only limited information are available on the long-term consequences of treatment<sup>1</sup>, although patients still experience frequent perturbing symptoms that can highly influence adherence to antiretrovirals<sup>13</sup> and quality of life<sup>14</sup>, as well as contribute to the emergence and spread of drug-resistant viruses.

Cohort studies have been instrumental in providing important knowledge on these aspects of HIV infection as they allow the longitudinal surveillance and recording of events along time and are therefore a central model of study to describe the complete picture of disease history, whether under treatment or not. During the last 15 years, European HIV researchers have been particularly active to create new as well as expand existing cohorts in a particularly suitable environment where HIV care is publicly funded and concentrated in a limited number of highly specialised clinical settings. In this context, results of a new cohort, like the Spanish cohort of naïve HIV-infected patients (CoRIS), are to be especially acknowledged<sup>15</sup>. By including a large number of patients during a recent period, and building a biobank, CoRIS may be considered as an important platform for the study of HIV infection currently and in the future.

As in the CoRIS Study, successful HIV observational cohorts like the MACS<sup>16</sup> in the USA or EuroSida<sup>3</sup>, ICONA<sup>13</sup>, UK-CHIC<sup>17</sup>, ATHENA<sup>7</sup>, the Swiss HIV cohort<sup>2</sup>, the ANRS CO3 Aquitaine cohort<sup>18</sup>, or the ANRS CO4 FHDH cohort<sup>19</sup> in Europe have set up their programs in close collaboration between clinical and epidemiological/biostatistical research groups. While the former make a major input in the formulation of hypotheses and scientific questions and they actively promote the implementation of the results of research into clinical and public health practice; the latter undertake the creation, management and maintenance

of appropriate databases and they enable the cohort to develop a scientific agenda on epidemiological aspects and innovative methodological approaches to help address relevant questions. Collaborations with virologists, immunologists, and pharmacologists are also very important to develop a true multidisciplinary approach of the scientific agenda, with complementary skills and experience, and to work on the current scientific issues and those of major public health importance.

While conveying such important strengths, individual cohorts are however limited by two aspects: firstly, their size may be limited to make robust comparisons either on rare events like those defining disease progression or adverse effects of therapy, or on specific populations like older individuals or seroconverters. Secondly, cohorts may be restricted by their site recruitment and it may be difficult to extrapolate results among larger populations of other geographical locations. When scientific questions necessitate very large sample size, collaborations of individual cohorts may maximise data usage and provide faster and more robust answers. Again, the leadership of European researchers has been in developing successful collaborations addressing current questions concerning HIV infection through a multidisciplinary approach. If we focus our review on the study of HIV infection in adults, the major collaborations include: the Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE) Collaboration, the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D Study), and the Antiretroviral Therapy Cohort Collaboration (ART-CC). They are focused on a specific population or on a scientific question and have yielded landmark results with important consequences for clinical practice in the past five years.

CASCADE is a collaboration of 23 cohorts that include more than 16,000 individuals with well-estimated dates of HIV seroconversion from Europe, Australia and Canada. CASCADE has quantified the impact of the introduction of HAART on progression to AIDS and survival of HIV-infected patients<sup>20</sup>. The collaboration has also shown the difference in the distribution of causes of death following the introduction of HAART<sup>21</sup>. These observations help prioritise decision-making on diagnosis and prevention in the daily case management.

D:A:D, a collaboration of 11 cohorts following more than 23,000 HIV-infected individuals in Europe, the USA and Australia, has identified the presence of multiple known risk factors of cardio-vascular disease among HIV-infected patients, especially in older individuals<sup>22</sup>. In addition, this collaboration has shown that the risk of coronary disease was associated only partly to antiretroviral treatment and mostly explained by traditional risk factors<sup>11</sup>. Therefore, the benefit of cART still outweighs the increased risk of

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cardio-vascular disease associated with antiretrovirals, and practitioners should pay specific attention to traditional risk factors (tobacco consumption, dyslipidemia, diabetes) in the case management of these patients.

ART-CC, a collaboration of 13 cohort studies from Europe and North America, showed that CD4<sup>+</sup> cell count at initiation of cART remained a dominant prognostic factor, in addition to plasma HIV RNA<sup>23</sup>. In the following work, the current CD4<sup>+</sup> cell count and plasma HIV load, but not values at baseline, were strongly associated with subsequent disease progression in addition to age, injection drug use and AIDS stage<sup>24</sup>, underlining the importance of starting with highly potent antiretrovirals and promoting high observance to this treatment.

These results raise the question whether a long-term exposure to antiretrovirals will result in sustained improvements given the potential for therapy failure following difficulties with adherence, the emergence of resistance, and the development of adverse drug reactions. Continual monitoring of changes along time and assessment of their potential impact on long-term outcome should be pursued and even, strengthened.

Given these challenges, a new collaboration called COHERE (Collaboration of Observational HIV Epidemiological Research Europe) has started in 2006 with the mission to conduct epidemiological research on the prognosis and outcome of HIV-infected people from across Europe including pregnant mothers, children, and adults. This new collaboration will focus on scientific questions requiring a large sample size of patients which the contributing cohorts cannot answer individually and which do not overlap with existing collaborations between participating COHERE cohorts.

The first steps of a global collaboration are therefore accomplished, based on trust and transparency, and hopefully all partners will now feel comfortable to move forward with a unified governance structure planning for the longer-term development of observational HIV epidemiological research in Europe. In addition to the identification of areas of common scientific interest, such a unified governance structure should help improve standardisation of data collection and coding which are essential for collaborations to yield powerful and robust results, and should also promote training among all partners.

Such a global collaboration can be successful only if mechanisms are put in place that respect the huge amount of work to collect data of high quality accomplished by participating cohorts, prevent from competing with research projects or funding and share the different tasks required. No doubt that European HIV researchers as a group will be innovative enough to challenge this evolution, as they have shown their significant ability to maintain individual cohorts and even create new ones, like the CoRIS cohort<sup>15</sup>.

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