Establishing a Cohort of Pediatric Non-Progressors (PHASE TWO)
Concept Sheet for an MR IeDEA Project

Background

A subset of individuals living with HIV are able to maintain various degrees of control of HIV replication while conserving healthy CD4 counts for prolonged periods of time in the absence of ART, but long-term non-progression (LTNP) and viremic control is less well described in HIV-infected children compared to adults. Moreover, some data suggest that the mechanisms of non-progression in perinatally HIV-infected children may be distinct from those found in adults. There have been very few characterizations of "pediatric non-progressors" (PNP) to assess non-pathogenicity as well as investigate the relative contribution and interplay of various host and viral mechanisms.

Long-term non-progression and viremic control is less well described in HIV-infected children. Disease progression among perinatally infected children is more rapid compared to adults; over 50% of perinatally infected children die by the age of 2 in the absence of treatment compared to median AIDS-free survival of 11 years among ART-naïve HIV-infected adults.[1,2] As in adults, there is a subset of perinatally infected children (~10%) who are able to maintain normal-for-age CD4 counts and remain clinically healthy throughout childhood (roughly to ages 6 to 8 years),[3-5] although studies of these pediatric non-progressors (PNPs) are rare and hampered by heterogeneous definitions and study designs (as in adults) as well as small sample sizes given the concentration of the pediatric HIV epidemic outside of North America and Europe. Still, studies suggest a number of potential host and viral mechanisms. Viral factors include alterations in HIV Nef-induced cytotoxicity, downregulation of CD4 and MHC-1, fitness attenuating VC and Vif mutations.[6,7] Host factors include co-receptor tropism and other host restriction factor mutations,[8] higher T cell activation and counts of helper and cytotoxic T cells, of naïve and memory cell subsets,[3] higher CTL-induced selection pressure in MHC-restricted epitopes,[9] polyfunctionnal HIV-specific CD8 T cell reponses, and high levels of anti-Nef antibodies.[10] Importantly, data suggest that the mechanisms of nonprogression in children may be distinct from those found in adults. For example, while HLA class I alleles (e.g., HLA-B*27 or HLA-B*57) are associated with elite control in adults,[11] the data among children are conflicting.[12-15] Additionally, high CD4 counts and immune activation is associated with low viral loads in adult elite controllers; however, studies among children find that pediatric nonprogression and high CD4 counts are typically associated with persistent high viral loads.[3,16,17] Alongside low systemic immune activation found in one study on PNP,[16] the PNP phenotype may exhibit characteristics more similar to non-pathogenic SIV infection found in sooty mangabeys than non-pathogenic HIV infection in elite controllers.[18]

There have been very few characterizations of PNP to assess the true rate of non-pathogenicity type (i.e. non-progressor/sooty mangabey type or elite controller type) as well as to assess the relative contribution and interplay of various host and viral mechanisms. There are even fewer longitudinal follow-ups of these children to assess long-term outcomes and factors associated with loss or maintenance of non-progressor status. Elucidation of mechanisms associated with non-pathogenicity may be crucial to inform strategies and interventions including vaccine or

therapeutic approaches and is of high scientific interest to bodies such as the National Institutes of Health (internal communication).

Objectives

Given the rare nature and low frequency of the PNP phenotype (<10%), a large cohort of HIV-infected children is needed to provide access to and identify a sufficient number of PNP to enable meaningful observations. Across its seven regions, the IeDEA pediatric cohort represents the largest cohorts of HIV-infected children in the world and provides a unique opportunity to identify PNP and study the mechanisms associated with the PNP phenotype. After using the existing dataset (MR104) examining the retrospective cohort data for children pre-ART prior to 2017, enrolled in HIV care before the age of 10 years (as a proxy for perinatally acquired HIV) and describing HIV-infected children who reached adolescence without starting ART, this concept aims to assess the feasibility of establishing an IeDEA PNP cohort across the seven IeDEA regions among which to examine the prevalence of the PNP phenotype and associated host and viral factors, as well as long-term clinical, immunological, and virological outcomes. **To answer critical questions around PNP, as well as to contribute to much-needed insights in the quests to develop an HIV cure, we now propose to create a nested cohort of sites within global IeDEA that could recruit potential PNP, perform prospective evaluations including collection of additional biological specimens, and have the capacity for future prospective evaluations involving PNP.**

Methods

Determine the feasibility and provide proof of concept for using the data from the descriptive cohort dataset to establish an active, multiregional sub-cohort of children in IeDEA that have potential to be PNP and for whom further evaluation could be conducted.

1. ***Feasibility and Implementation Evaluation***

Establishing a PNP cohort within IeDEA will require a **detailed implementation plan** for operationalizing this network across IeDEA's global regions. The implementation plan will outline and allow for preparatory activities, including training, to determine the ability of sites in each region to trace youth described in the retrospective dataset, as well as their clinical and research capacity to conduct detailed evaluations that include collecting, processing, storing, and shipping biological specimens. We will need to determine sites' protocols on CD4/viral load testing and ART initiation and catalog any existing biospecimens or potential to collect biospecimens for these children/adolescents/young adults. In addition, we will critically reviewing ethical concerns and procedures relevant to cohort assembly in each region and their specific clinical programs.

Site surveys to assess the feasibility of such a study and what data is (or could be) available (e.g., number of ART-naïve children who entered into HIV care/had HIV diagnosis before the age of 10 years, number of HIV-infected children followed, protocols on CD4/viral load testing ART initiation, ability to trace and recruit potential study participants, and blood sample storage, etc.) will be done. Draft survey questionnaire is attached as an appendix at the bottom of this concept sheet. The survey assessment will be combined with interviews of key regional

leads for pediatric, adolescent and young adult care within the sites to attempt to determine which sites would be likely to participate in the prospective cohort evaluation, as well as the capacity and potential of each site, including study population/size and data collection procedures.

2. Establishing Proof of Concept Pilot Cohort

We will establish [PNP Pilot Cohort] as the framework for a nested study cohort of PNP within the global IeDEA consortium through which standardized, prospective data related to the host and viral mechanisms of PNP can be collected and examined. PNP Pilot Cohort will represent a network of LMIC sites from across IeDEA's global regions that have the capacity to recruit, evaluate, and retain PNP as study participants. To establish this framework, each of IeDEA's 6 participating global regions will select 1-4 clinical sites that can initially recruit cohorts of 20-50 potential PNP per region, testing the ability to trace, contact, consent/assent, and evaluate participants previously identified in the retrospective data analysis. Local ethics board approval for these protocols will need to be obtained prior to study implementation. After the consenting process, we will administer an assessment of each participant's demographic, clinical, virologic, and treatment characteristics. Then, we will collect the samples indicated. Contact information and permission to stay in touch with the participants and their families on a long-term basis will be sought as part of this protocol. We will work with sites to identify and develop mechanisms to consistently collect and store biological samples (e.g., full blood, plasma and/or dried blood spots). The detailed implementation plan developed above will determine the initial scope for the biological specimens to be collected. Constructing an appropriate study database and data management protocols for these data will be part of the pilot proof of concept.

3. Planning Phase

The PNP cohort leads, in partnership with the leaders of the clinical and research sites for the pilot cohort, will prepare an application for additional funding to assemble, evaluate, and maximize an IeDEA PNP cohort, including their phenotype, associated host and viral factors, and potential mechanisms of non-progression. In this phase, various funding options will be considered carefully and the most appropriate mechanism for funding this multicenter work will be determined.

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