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Identification and characterization of HIV positive Ethiopian elite controllers in both Africa and Israel

YK Kiros[#1], **H Elinav**[#2], **A Gebreyesus**[1], **H Gebremeskel**[1], **J Azar**[3], **D Chemtob**[4], **H Abreha**[1], **D Elbirt**[5], **E Shahar**[6], **M Chowers**[7], **D Turner**[8], **Z Grossman**[2], **A Haile**[1], **RE Sutton**[9], **SL Maayan**[10], and **D Wolday**[1]

[1]Mekelle University College of Health Sciences, Mekelle, Tigray, Ethiopia

[2]Clinical Microbiology and Infectious Diseases Department, Hadassah University Medical Center, Jerusalem, Israel

[3]Internal Medicine Division, Hadassah University Medical Center, Jerusalem, Israel

[4]Department of Tuberculosis and AIDS, Ministry of Health, Jerusalem, Israel

[5]The Allergy, Clinical Immunology and AIDS Unit, Kaplan Medical Center, Rehovot, Israel

[6]Institute of Allergy, Immunology and AIDS Rambam Medical Center, Haifa, Israel

[7]Infectious Diseases Unit, Meir Medical Center, Kfar Saba, Israel

[8]Crusaid Kobler AIDS Center, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel

[9]Division of Infectious Diseases, Department of Medicine, Yale University School of Medicine, New Haven, CT, USA

[10]Division of Infectious Diseases, Barzilai Medical Center, Ashkelon, Israel

[#] These authors contributed equally to this work.

Abstract

Objectives—HIV elite controllers (ECs) are a unique subgroup of HIV-positive patients who are long-term virologically suppressed in the absence of antiretroviral treatment (ART). The prevalence of this subgroup is estimated to be < 1%. Various cohorts of ECs have been described in developed countries, most of which have been demographically heterogeneous. The aim of this study was to identify ECs in two large African cohorts and to estimate their prevalence in a relatively genetically homogenous population.

Methods—We screened two cohorts of HIV-positive Ethiopian patients. The first cohort resided in Mekelle, Ethiopia. The second was comprised of HIV-positive Ethiopian immigrants in Israel. In the Mekelle cohort, ART-naïve subjects with stable CD4 counts were prospectively screened using two measurements of viral load 6 months apart. Subjects were defined as ECs when both measurements were undetectable. In the Israeli cohort, subjects with consistently undetectable

Correspondence: Prof Shlomo L. Maayan, Barzilai Medical Center, Ashkelon 7830604, Israel. Tel: 972-8-86746952; fax: 972-737314904; shlomom@bmc.gov.il.

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viral loads (mean of 17 viral load measurements/patient) and stable CD4 count > 500 cells/μL were defined as ECs.

Results—In the Mekelle cohort, 16 of 9515 patients (0.16%) fitted the definition of EC, whereas seven of 1160 (0.6%) in the Israeli cohort were identified as ECs ($P = 0.011$).

Conclusions—This is the first large-scale screening for HIV-positive ECs to be performed in entirely African cohorts. The overall prevalence of ECs is within the range of that previously described in developing countries. The significant difference in prevalence between the two cohorts of similar genetic background is probably a consequence of selection bias but warrants further investigation into possible environmental factors which may underlie the EC state.

Keywords

elite controllers; Ethiopia; HIV; Israel

Introduction

Although highly active antiretroviral therapy (HAART) has transformed HIV sero-positivity into a manageable chronic disease and is being implemented throughout Ethiopia [1], treatment is not curative and life-long therapy is required. For the vast majority of infected untreated individuals, HIV eventually causes CD4 T-cell depletion and severe immunodeficiency, resulting in morbidity and mortality. However, in a small proportion of individuals (< 1%), termed elite controllers (ECs), viral replication is suppressed to undetectable levels (< 50 to < 500 copies/mL), with peripheral CD4 T cells maintained in the absence of antiretroviral therapy (ART) [2–5]. Studies have indicated that defective HIV does not explain the clinical status of most EC patients, who appear to have an intrinsic ability to control HIV. While the mechanisms of viral containment remain largely unknown, a number of key features have been associated with elite control, including human leucocyte antigen (HLA)-associated antigens presentation and HIV-1 specific-CD8 T-cell responses against viral gene products, polyfunctional immune responses to HIV antigens, with greater degranulation and release of perforin and granzyme B proteins, and CD4 T cells that produce higher levels of macrophage inflammatory protein (MIP) chemokines [2–4].

As understanding mechanisms of suppression of HIV replication is a potential gateway to new therapeutic options or even a cure for HIV infection, the field of EC research has burgeoned to produce over 500 publications, although the definition of EC varies between cohorts and studies. Some studies required three or more viral load (VL) determinations below the limit of detection spanning 12 months or more, while other studies defined a person as an EC only when > 90% of his VL measurements were below the limit of detection over 10 years [5]. Unfortunately, VL measurements are not routinely performed in most African HIV centres, and thus ECs cannot be easily identified and the prevalence of this patient group in different African countries is unknown. The aim of this study was to describe two cohorts of HIV-positive Ethiopians residing in two different countries and to measure the prevalence of the EC phenotype in each.

Materials and methods

We identified two different cohorts of HIV-positive patients originating in Ethiopia: the General Mekelle cohort residing in Ethiopia and the General Ethiopian-Israeli immigrant cohort residing in Israel, and we identified EC patients in these two cohorts.

The General Mekelle cohort

For the purpose of identifying ECs in Ethiopia, we used a pool of all HIV-positive patients > 18 years of age who were diagnosed in the Mekelle region, Tigray Province, Ethiopia between the years 2000 and 2015. These patients were consistently referred for follow-up at six regional ART clinics in the province. Initial diagnosis of HIV infection was performed at antenatal clinics, at voluntary counselling and testing (VCT) clinics, prior to obtaining a visa and during hospitalization.

Identification of EC patients in the General Mekelle cohort—We first reviewed all the files of treatment-naïve patients. Patients who were followed for at least 5 years up to 1 August 2016 and had a stable CD4 count > 500 cells/μL throughout their follow-up were eligible for the next step of screening by VL measurement. For VL measurement we used real-time polymerase chain reaction (PCR) (NucliSENS Easy Q; BioMerieux, Boxtel, Netherlands). Patients who had a VL < 50 HIV-1 RNA copies/mL on the first test were tested once again at least 6 months later. Those whose VL remained < 50 copies/mL at the repeat testing were defined as ECs. Patients were excluded from initial CD4 screening if they had been exposed to ART for any duration of time, or had an indication for HIV therapy based on National Ethiopian Guidelines (e.g. CD4 count < 500 cells/μL, stage 3/4 disease, pregnancy or active tuberculosis).

The General Ethiopian-Israeli cohort

The General Ethiopian-Israeli cohort included all HIV-positive Ethiopian immigrants aged > 18 years, diagnosed between 1998 and 2015 and reported to the National Israel Registry. Routine HIV screening was performed in the few months following immigration as part of the Israeli health policy for legal immigrants from highly endemic areas for HIV [6].

Identification of EC patients in the General Ethiopian-Israeli cohort—Medical records of HIV-positive Ethiopians followed in six regional hospital-based ART clinics in Israel were reviewed. Patients were defined as ECs if they had consistently undetectable VLs since diagnosis until 1 December 2016, had a CD4 count > 500 cells/μL, and were not on ART. Patients who had occasional VL blips up to 200 copies/mL were still considered as ECs. We included patients who were exposed transiently to antiretrovirals during pregnancy.

Statistical analysis

In order to compare the prevalence of ECs in the General Mekelle cohort to that in the General Ethiopian-Israeli cohort, we used the measure of mean person-years of observation (PYO). Only patients in active follow-up were included in PYO calculations, while patients who were lost to follow-up, who transferred out or who died were excluded. PYO was thus calculated for 1012 HIV-positive patients followed in the Mekelle General cohort and for

1160 patients in the General Ethiopian-Israeli cohort (n = 1160 patients). Fisher's exact test was used to compare the prevalences of ECs in the two cohorts.

Results

The General Mekelle cohort

Overall, 15 619 HIV-positive patients were identified in the Mekelle region from 2000 to 2016, and 9515 patients were being actively followed on 1 August 2016. Of the remainder, 6104 were lost to follow-up (n = 1264; 8%), were transferred out (n = 3104; 19.8%) or died (n = 1736; 11.1%). Of the remaining 9515 patients being actively followed, 6061 (63.6%) were women and 3454 (36.3%) were men, with a mean age of 28.4 years [standard deviation (SD) 8.5 years] and a mean CD4 count at diagnosis of 830 cells/μL (SD 55 cells/μL). Mean follow-up time, as calculated in one of the six ART clinics (n = 1012 patients), was 4.6 years (SD 2.4 years) (Table 1).

Identification of EC patients in the General Mekelle cohort—Of the 9515 patients, 1941 were not on ART and asymptomatic. Of these, we identified 45 patients who had been followed actively for at least 5 years, with a stable CD4 count > 500 cells/μL over that period. These patients underwent VL testing. Of these 45, 16 patients had a VL < 50 copies/mL, one patient had a 50 < VL < 100 copies/mL, six patients had 100 < VL < 1000 copies/mL, and 22 patients had a VL > 1000 copies/mL. The 16 patients who initially had a VL < 50 copies/mL underwent repeat VL testing after 6 months and all still had a VL < 50 copies/mL. They were considered ECs. The 16 EC patients (0.16% of the cohort) were all women, with a mean age of 31.56 years (SD 2.39 years), a median age of 30 years [interquartile range (IQR) 10 years] and a mean CD4 count of 907 cells/μL. This EC cohort was followed for a mean of 6.43 PYO (SD 1.78 PYO) and a median of 6.6 years before they were identified as ECs.

The General Ethiopian-Israeli cohort

A total of 1311 HIV-positive Israelis of Ethiopian origin and age > 18 years were reported to the National Israel Registry. Of these 1311 patients, 151 (11.5%) had died. Of the remaining 1160 patients, 689 patients were women (59.3%) and 471 (40.6%) were men, with a mean age of 37.4 (SD 11.7) years. The mean follow-up time for the 1160 patients was 9.34 PYO (SD 2.9 PYO) The mean initial CD4 count (available for only 309 of 1160 patients; 26.6%) was 281 cells/μL (SD 205 cells/μL) (Table 1).

Identification of EC patients in the General Ethiopian-Israeli cohort—Among the Ethiopian-Israeli cohort of 1160 patients, we identified seven (0.6%) patients (five women and two men) who fitted the diagnosis of EC with consistent undetectable VL during their follow-up. These EC patients had a mean age of 51.71 years (SD 2.68 years) and a median age of 51.00 years (IQR 8 years). The mean follow-up of the seven patients identified as ECs was 13.1 PYO (SD 2.93 PYO) with a mean of 17 undetectable VL measurements per patient over the years of follow-up. The mean CD4 count during the follow-up of the seven EC patients was 711 cells/μL (SD 127 cells/μL).

Thus, in the General Mekelle cohort, 16 of 9515 patients (0.16%) were identified as ECs. In the General Ethiopian-Israeli cohort, seven of 1160 patients (0.6%) were identified as ECs. Differences were statistically significant ($P = 0.011$).

Discussion

In this study, we screened two cohorts of East African origin and demonstrated that the EC rates in this population ranging from 0.16% to 0.6% similar to rates described in genetically heterogeneous cohorts in developing countries. There are multiple definitions of the HIV-positive EC state. Olsen *et al.* [5] examined 10 EC definitions in a large cohort of European HIV-positive individuals (CASCADE collaboration - Concerted Action on SeroConversion on AIDS ans Death in Europe), analysing the hazard ratio for progression to AIDS, death, ART initiation, or CD4 count decline to < 350 cells/μL. Of the 10 definitions of EC, four were found to predict a better outcome with low rates of HIV progression in ECs. One of the best predictors was a definition using two consecutive VL measurements of < 50 copies/mL in a time interval of > 6 months. Other definitions required three consecutive undetectable HIV RNA measurements for > 6 months, and one defined EC patients as those with > 90% of VL measurements being < 400 copies/mL over 10 years. These studies confirm the rarity of ECs and also suggest that over time some degree of progression eventually occurs in the great majority of EC patients. The challenge of carrying out an EC project in a developing country led us to choose the more permissive definitions which was the most achievable in the Ethiopian setting in terms of availability of measurements: VL < 50 copies/mL over a period of 6 months. We used a somewhat stricter definition for the Ethiopian-Israeli EC cohort, as VLs were available for many years of follow-up. The Mekelle and Ethiopian-Israeli cohorts were similar in gender distribution (63% women in the Mekelle cohort; 59% women in the Ethiopian-Israeli cohort; Table 1). However, important differences were noted. The Mekelle cohort was significantly younger (mean age 28.4 years; SD 8.5 years) than the Ethiopian-Israeli cohort (mean age 37.4 years; SD 11.7 years) ($P < 0.0001$), with a significantly shorter follow-up time, as reflected in the mean PYOs (4.36 years for the Mekelle cohort versus 9.34 years for the Ethiopian-Israeli cohort; $P < 0.0001$). The Mekelle cohort, surprisingly, had a higher mean initial CD4 count of 830 cells/μL in comparison to 281 cells/μL in the Ethiopian-Israeli cohort ($P < 0.0001$). In addition, the identified EC patients within the cohorts were followed for a shorter time in the General Mekelle cohort (PYO 6.43 years) than in the General Ethiopian-Israel cohort (PYO 13.1 years), although differences in PYO were not statistically significant.

The rate of ECs was 0.6% for the General Ethiopian-Israeli cohort and 0.16% for the General Mekelle cohort ($P = 0.011$). This statistically significant difference could not be explained by genetic differences between Mekelle Ethiopians and Ethiopian immigrants to Israel, as great similarity in the genetics of Beta Israel Ethiopian Jews and local Ethiopians was described previously [7,8]; neither could it be explained by the longer follow-up of EC patients in the Israeli cohort. The most likely explanation for the difference is a screening bias which originated from the Israeli policy of mandatory screening of all immigrants to Israel for HIV. Thus, many asymptomatic HIV carriers were diagnosed upon immigration and were followed for many years. A similar mandatory screening policy does not exist in Ethiopia. In Ethiopia, mandatory screening exists only at blood banks [9] and voluntary

screening is highly encouraged. Major reasons for HIV testing in Ethiopia are pregnancy, immigration, AIDS-defining illnesses (such as tuberculosis) and voluntary testing at HIV counselling and testing (HCT) clinics [10]. It is thus likely that the true rate of ECs in Ethiopia is higher but these patients go undiagnosed.

Other possible explanations for the difference in EC rate may lie in differences in immigrants' nutrition as compared with local nutrition in the African setting and in the prevalence of intestinal parasites and helminths which are endemic in sub-Saharan Africa. Changes in the nutritional environment have been implicated in the development of new diseases among immigrants and regression of others as the environment changes [11,12]. Ethiopian immigrants in Israel are exposed to Westernized nutrition which is very different from the traditional Ethiopian nutrition and thus presumably modifies their microbiome which has been shown to influence the immune system [13]. Additionally, the chronic parasitic burden in the Ethiopian setting has been suggested to be a factor associated with immune dysregulation and activation [14]. Deworming seems to lead to decreased immune regulation and increased immune responsiveness [15], although its effect in HIV/AIDS has been a matter of controversy [16]. It is conceivable that a reduction in overall immune activation caused by the modified nutrition and environment following immigration may contribute to the maintenance of the EC state and may thus explain our findings of a higher prevalence of EC among HIV-positive immigrants in Israel. The General Ethiopian-Israeli cohort had resided in a new environment in Israel for > 9 years. It is likely that treatment for intestinal parasites was offered whenever eosinophilia was noted [17]. In contrast, individuals in the General Mekelle cohort had resided in their native environment for a mean of over 28 years (i.e. the mean age of that cohort). Sub-Saharan Africa is an endemic environment for intestinal parasites, which usually go untreated except in deworming campaigns [16]. The lower CD4 T-cell levels in the Israeli cohort compared with the Mekelle cohort do not support the hypothesis that environmental and nutritional factors account for the difference in the frequency of HIV-positive ECs between the two cohorts. Improved nutritional status and lower parasite burden, if anything, should be associated with higher CD4 T-cell levels.

There are important limitations to our study. As a con-sequence of the lack of skilled manpower we were unable to measure PYO in all 9515 patients in the General Mekelle cohort. We assume that the PYO we measured in one of the six ART clinics in Mekelle (representing 10.6% of the entire Mekelle cohort) actually represents the PYO of the entire cohort. Another limitation relates to the mandatory HIV screening performed for all immigrants from Ethiopia to Israel. This may have created a selection bias towards detecting HIV carriers at an earlier stage than those detected at VCT clinics in Ethiopia. This is offset, however, by the fact that initial CD4 count in the General Ethiopian-Israeli cohort was available for only 26% of patients and may not be representative of the entire cohort.

Lastly, the recommendations of the updated US, European and World Health Organization (WHO) guidelines to begin HAART regardless of CD4 count and VL and as early as possible stem from the Strategic Timing of Anti-Retroviral Therapy (START) study [18] and are expected to result in a substantially reduced rate of diagnosis of ECs in the future, as most EC candidates will not meet any of the strict EC definitions described above. Thus, the

window of opportunity to study factors in ECs that slow the natural progression of HIV infection is slowly closing.

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References

1. Asseffa Y, Jerene D, Lulsegad S, Ooms G, Van Damme W. Rapid scale up of antiretroviral treatment in Ethiopia: successes and system wide effects. PLoS Med 2009; 6: e100056.
2. Gonzalo-Gil E, Ikediobi U, Sutton RE. Mechanisms of virologic control and clinical characteristics of HIV+ Elite/Viremic controllers. Yale J Biol Med 2017; 90: 245–259. [PubMed: 28656011]
3. Walker WE, Kurscheid S, Joshi S et al. Increased levels of macrophage inflammatory proteins result in resistance to R5-Tropic HIV-1 in a subset of elite controllers. J Virol 2015; 89: 5502–5514. [PubMed: 25740989]
4. Blankson JN. Effector mechanisms in HIV-1 infected elite controllers: highly active immune responses? Antiviral Res 2010; 85: 295–302. [PubMed: 19733595]
5. Olsen AD, Meyer L, Prins M et al. An evaluation of HIV Elite controller in a large seroconverter cohort collaboration. PLoS ONE 2014; 19: e86719.
6. State of Israel, Ministry of Health. Medical absorption of new immigrants from Ethiopia – update. Directive of the Head of the Department of Epidemiology No. 45/00 from 30.08.2000 and update No. 9/01 from 24.01.2001.
7. Bonne-Tamir B, Gross Y, Ashbel S, Goldwitch Z. Genetic polymorphisms among Ethiopian Jews in Israel. Gene Geogr 1987; 1: 1–8. [PubMed: 3154107]
8. Lovell A, Moreau C, Yotova V et al. Ethiopia: between Sub-Saharan Africa and Western Eurasia. Ann Hum Genet 2005; 69: 275–287. [PubMed: 15845032]
9. Ethiopia National guidelines for comprehensive HIV prevention, care and treatment Available at https://aidsfree.usaid.gov/sites/default/files/ethiopia_natl_gl_2014.pdf (accessed 02 January 2018).
10. Guidelines for HIV counseling and testing in Ethiopia Available at www.who.int/hiv/topics/vct/ETH_HCT_guidelinesJune26_2007clean.pdf (accessed 02 January 2018).
11. Eamranond PP, Hu H. Environmental and occupational exposures in immigrant health. Environ Health Insights 2008; 1: 45–50. [PubMed: 21572847]
12. Trostler N Health risks of immigration: the Yemenite and Ethiopian cases in Israel. Biomed Pharmacother 1997; 51: 352–359. [PubMed: 9436530]
13. Yasmine B, Timothy H. Role of the microbiota in immunity and inflammation. Cell 2014; 157: 121–141. [PubMed: 24679531]
14. Brokow G, Leng Q, Weisman Z et al. Chronic immune activation associated with intestinal helminth infections results in impaired signal transduction and anergy. J Clin Invest 2000; 106: 1053–1060. [PubMed: 11032865]
15. Wammes LJ, Hamid S, Wiria AE et al. Community deworming alleviates geohelminth-induced immune hyporesponsiveness. Proc Natl Acad Sci USA 2016; 113: 12526–12531. [PubMed: 27791067]
16. Lankowski AJ, Tsai AC, Kanyesigye M, Bwana M. Empiric deworming and CD4 count recovery in HIV-infected Ugandans initiating antiretroviral therapy. PLoS Negl Trop Dis 2014; 8: e3036. [PubMed: 25101890]
17. Berger SA, Schwartz T, Michaeli D. Infectious disease among Ethiopian immigrants in Israel. Arch Intern Med 1989; 149: 117–119. [PubMed: 2912401]
18. The INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med 2015; 373: 795–807. [PubMed: 26192873]

Table 1

Demographic data, person-years of observation (PYO) and elite controller (EC) patient details for the General Mekelle and General Ethiopian-Israeli cohorts

	Mekelle cohort	Ethiopian-Israeli cohort
Years of follow-up	2000–2016	1998–2016
Total number of patients diagnosed	15 619	1311
Lost to follow-up/died (*n*)	6104	151
In active follow-up (*n*)	9515	1160
Age at diagnosis (years) [mean (SD)]	28 (8.5)	37 (11.7)
Gender (F/M) (%)	63/36	59/41
Initial CD4 count (cells/μL) [mean (SD)] *	830 (55)	281 (205) ‡
PYO in the general cohort (mean)	4.6 †	9.34
ECs (*n*)	16	7
PYO in the EC cohort (mean)	6.93	13.7

* *n* = 9515 in active follow-up.

† *n* = 1012 (at Ayder antiretroviral therapy clinic; see text).

‡ Available for only 309 of 1160 patients (26.6%) in active follow-up.

F, female; M, male; SD, standard deviation.