BRIEF REPORT

Immunovirologic Control 24 Months After Interruption of Antiretroviral Therapy Initiated Close to HIV Seroconversion

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Background: There is interest in whether a short course of combination antiretroviral therapy (cART) at the time of human immunodeficiency virus (HIV) seroconversion could induce long-term immunologic control after its interruption. We aimed to determine the time of virologic rebound after interruption of treatment initiated close to HIV seroconversion and to identify potential cases of posttreatment controllers (PTCs) in the CASCADE (Concerted Action on Seroconversion to AIDS and Death in Europe) Collaboration.

Methods: Prospective cohort study nested within the CASCADE database of routinely collected data about patients with HIV with well-estimated date of HIV seroconversion from Europe, Canada, and Australia in the post-cART era. Participants were individuals who interrupted successful cART initiated within 3 months of HIV seroconversion. The main outcome was loss of PTC status, defined as the earlier date of virologic rebound (first of 2 consecutive measurements showing HIV RNA levels >50 copies/mL) or reinitiation of any ART after cART interruption.

Results: Median time to loss of PTC status in 259 eligible individuals was 1.7 months. Eleven patients did not experience virologic rebound by 24 months after treatment interruption.

Conclusion: Most patients experience virologic rebound soon after cART interruption; however, although PTCs are rare, the results of this study confirm their existence.

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THERE IS INTEREST IN whether intervention with a short course of combination antiretroviral therapy (cART) at the time of, or shortly after, human immunodeficiency virus (HIV) seroconversion could induce long-term immunologic control following its interruption, reducing the need for overall ART exposure.

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Studies[1-4] have shown that viral control is maintained in some patients who receive a short course of cART during primary HIV infection, even after interruption of cART, suggesting that the viral reservoir might not be replenished after interruption. Recently, Hocqueloux et al[2] reported on behalf of the HIV Reservoir Working Group on 5 patients, described as *posttreatment controllers* (PTCs), who displayed sustained immunovirologic control after discontinuation of short-course cART initiated in primary HIV infection (PHI). The frequency of PTCs (15.6%) was higher than expected, given that fewer than 0.5% of patients would be expected to achieve spontaneous control of HIV RNA, ie, without use of cART, according to the findings from other groups.[5,6]

Motivated by these findings, we aimed to explore whether similar PTC cases were present in CASCADE (Concerted Action on Seroconversion to AIDS and Death in Europe), a collaboration of cohorts of patients with well-estimated dates of HIV seroconversion from Europe, Australia, Canada, and Sub-Saharan Africa. All the eligible individuals are included in CASCADE cohorts from data collected routinely in clinical practice.

METHODS

From the CASCADE database, we extracted cases of individuals who met the following criteria: (1) less than 3 months between the last negative and first positive HIV antibody test re-

sults and/or laboratory evidence of acute HIV seroconversion (real-time polymerase chain reaction positivity in the absence of HIV antibodies or antigen positivity with <4 bands on a Western blot test), (2) early cART (within 3 months of HIV seroconversion and given for ≤3 months), (3) successful treatment (≥1 HIV RNA level <50 copies/mL within 6 months while receiving cART and with last HIV RNA level <50 copies/mL during cART), and (4) subsequent interruption of treatment. Interruption was defined as the absence of any ART for 30 days or less.

Using Kaplan-Meier methods, we estimated the median time from cART interruption to loss of PTC status, defined as the earlier date of cART reinitiation and the first of 2 consecutive HIV RNA levels of more than 50 copies/mL. Censoring occurred when a patient was lost to follow-up.

We performed 2 sensitivity analyses. Because the lower detection limit for some HIV RNA assays was above 50 copies/mL, analyses were repeated using a threshold of 400 copies/mL. Moreover, we reanalyzed these data using a definition of treatment interruption as 15 days without treatment.

All the cohorts in CASCADE received approval from their individual ethics review boards. Two ethics review boards deemed their cohort participants exempt from providing signed informed consent. Signed informed consent was obtained from all the other participants. Approval was also given by all the ethics review boards to pool anonymous data for analyses and dissemination.

RESULTS

Of 25 629 patients in CASCADE, we identified 259 who interrupted a successful cART regimen initiated within 3 months of HIV seroconversion between 1996 and 2009. Of these, 174 patients (67.2%) were infected via sex between men, and 44 women (17.0%) and 29 men (11.2%) were infected through sex between men and women. Median (interquantile range [IQR]) age at cART initiation was 34 (29-42) years, and median duration of cART was 1.3 (0.8-2.0) years followed by a median duration of cART interruption of 2.0 (0.5-4.2) years. Median (IQR) $CD4^+$ cell count and $\log_{10}$ HIV RNA at cART initiation were 556 (404-745) cells/μL and 4.5 (3.4-5.5) $\log_{10}$ copies/mL. Two hundred three patients (78.4%) initiated treatment with a combination containing a protease inhibitor; for 140 of these participants, this was a boosted protease inhibitor. During treatment interruption, the median number of HIV RNA measurements per patient was 14 (9-21) and the median interval between subsequent HIV RNA recordings was 3.1 (1.7-4.7) months. The median most recent $CD4^+$ count before interruption was 762 (602-970) cells/μL recorded 1 (0.03-3.0) month before interruption.

Among the 259 patients interrupting cART, 241 and 12 lost their PTC status because of virologic rebound and reinitiation of cART, respectively, and 6 were lost to follow-up. The probability of maintaining PCT status at 12 and 24 months after cART interruption was 8.2% (95% CI, 5.2%-12.2%) and 5.5% (95% CI, 3.1%-9.0%), respectively. Eleven individuals maintained PTC status 24 months after treatment interruption after receiving cART for a median (IQR) of 1.0 (0.7-1.5) year (**Figure**). Their median age was 29 (28-37) years, and 4 were women. They had been treated with an initial combination containing a boosted protease inhibitor (n=5), an unboosted protease inhibitor (n=2), and a nonnucleoside reverse transcriptase inhibitor (n=4), and their median $CD4^+$ count while not receiving treatment was 901 (764-1048) cells/μL. The characteristics of these 11 individuals and their treatment experience did not differ significantly from those of the overall study population of 259.

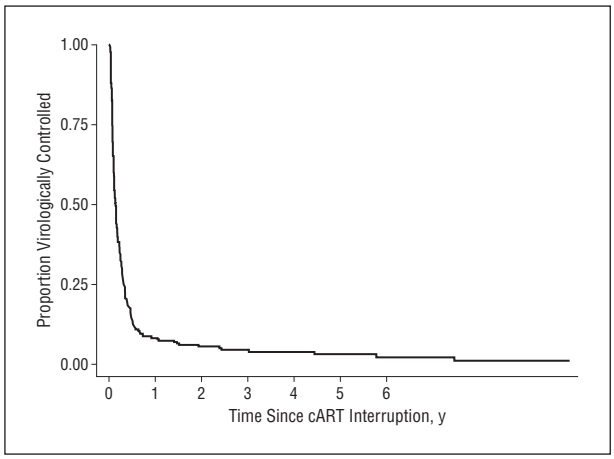

Figure. Kaplan-Meier estimate of the proportion of patients maintaining virologic control after interruption of short-course cART initiated within 3 months of HIV seroconversion. Loss of virologic control is defined as experiencing at least 2 consecutive HIV RNA levels of more than 50 copies/mL or reinitiation of cART. cART indicates combined antiretroviral therapy; and HIV, human immunodeficiency virus.

When we repeated the analysis using a 400 copies/mL cutoff limit for HIV RNA assays and then using a definition for interruption of 15 days without cART, 6.8% (95% CI, 4.3%-10.2%) and 5.1% (95% CI, 2.8%-8.4%) of the patients were estimated to maintain PTC status at 24 months after cART interruption, respectively.

COMMENT

Our findings confirm the existence of PTCs, although they are rare. These individuals experienced virologic control and high $CD4^+$ levels while not receiving treatment.

The proportion of the population estimated to be PTCs at 24 months in our study (5.5%) is substantially lower than that reported by Hocqueloux et al[2] (15.6%). This difference can be explained by variations in study design. Their inclusion was restricted to individuals who were not taking cART for at least 24 months, rather than to all those at risk of losing their PTC status after cART interruption. In this manner, individuals who remained event free (ie, retained PTC status) for less than 24 months were excluded from the risk set; therefore, a selection of healthier patients who did not need treatment for at least 24 months and therefore had a better virologic profile is likely to have been included. Our analyses allowed for the inclusion of all the individuals at risk of losing PTC status and provide a more accurate estimate.

Our study has some limitations. Given that most individuals received therapy before 2001, a nonnegligible proportion of eligible patients will have begun receiving combinations likely to be less potent than those started by patients recently initiating therapy, including those in the Hocqueloux et al study.[2] Moreover, the included

individuals had a short HIV test interval (interval between negative and positive HIV test dates) and were, therefore, more likely to be symptomatic and have poor prognosis.[7] If short-course treatment at HIV seroconversion was beneficial to induce immunovirologic control, both scenarios would have resulted in an underestimate of the proportion of PTCs. In addition, because our data are interval censored, we know the dates of clinic visits when these events were first observed rather than the exact time of cART interruption or loss of control; therefore, we may have underestimated or overestimated the proportion of patients losing PTC status. Furthermore, 12 individuals restarted cART before losing their PTC status, making it impossible to evaluate whether some, or even all, of them could have maintained their PTC status. Finally, the duration of cART before interruption in this study was relatively short (1.1 years). It may well be that, if our study included data from individuals who received treatment for longer times, we could have found a higher proportion of PTCs. Nevertheless, our study suggests that it is possible for some individuals receiving treatment for approximately 1 year to achieve viral control for more than 2 years after cART is interrupted.

Understanding of the long-term benefits of transient therapy at the time of PHI remains controversial. Treatment interruption, at least in chronic infection, is no longer recommended,[8] and the recent results from SPARTAC (Short-Pulse Anti-Retroviral Therapy at HIV Seroconversion)[4] have shown only a modest delay in disease progression after 48 weeks of cART in PHI. It is possible that the 11 individuals in our study who maintained PTC status 24 months after receiving cART for 1.0 year would have naturally controlled viral replication if they did not received treatment during early HIV infection. The question remains as to whether initiation of cART in PHI of longer duration could be of benefit in controlling viral replication, possibly through reducing the size of the viral reservoir, and in reducing lifetime exposure to ART. Although the detrimental consequences of discontinuing cART in chronic infection, driven by increases in inflammatory and coagulation markers, are well established,[9] there seems to be no evidence of similar risks associated with stopping cART in PHI.[10] The possibility of inducing long-term immunovirologic control by initiating ART at such an early stage of HIV infection is exciting; however, we believe that more data on PTCs from other cohorts, a better understanding of the mechanisms that underlie the dynamics in PHI, and evidence from randomized controlled trials are needed before treatment interruption in early infection can be recommended.

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