Integrase strand-transfer inhibitors for treatment of early HIV infection

A case series

Ramón Teira, MDa,∗, Mar Gutierrezb, Pepa Galindo, PhDb, Elisa Martínez, PhDb, Pepa Muñoz, PhDb, Belén de la Fuente, PhDb, Francisco Téllez, MDg, Marta Montero, PhDb

Abstract

This study evaluated whether the interval from the first clinic visit until the start of antiretroviral treatment (ART) was correlated with common parameters of immunological recovery among patients with early HIV infection (EHI).

We reviewed the medical records of patients with EHI who started ART using integrase strand-transfer inhibitors (ISTIs) within the first 6 months after diagnosis. Simple linear regression analyses were performed to determine whether the interval from the first visit to the start of ART was correlated with 1-year changes in CD4+ cell count, CD8+ cell count, CD4+ percentage, and CD4+/CD8+ ratio.

Fifty-three patients with probable or definite EHI started ART using ISTIs between April 2014 and August 2016. Forty-nine patients completed 1 year of follow-up, including 48 men. The routes of HIV transmission were 1 case of needle sharing, 5 cases of heterosexual activity, and 43 cases of men who had sex with men. None of the immunological recovery parameters were correlated with time to the start of ART (CD4+ cell count: R = .12, P = .42; CD8+ cell count: R = .107, P = .5; CD4+ percentage: R = .14, P = .34; CD4+/CD8+ ratio: R = .23, P = .14). Furthermore, subgroup sensitivity analyses failed to detect significant correlations based on definite or probable diagnoses, treatment using elvitegravir or dolutegravir, or the time from HIV diagnosis to ART initiation.

This series of EHI cases indicate that using ART with ISTI-based regimens is efficacious and well-tolerated. However, earlier initiation of treatment was not significantly correlated with common parameters of immunological recovery.

Abbreviations: AHI = acute HIV infection, ART = antiretroviral treatment, EHI = early HIV infection, ISTI = integrase strand-transfer inhibitors, VL = viral load.

Keywords: acute HIV infection, dolutegravir, early HIV infection, elvitegravir, integrase inhibitors

1. Introduction

The arbitrary 6-month interval after the first entry of HIV virions through a mucosal surface or a percutaneous event is referred to as “early HIV infection” (EHI). This interval includes a biologically well-defined short subperiod until antibodies are first detected in the serum (acute HIV infection; AHI) and a longer, complex, and biologically ambiguous subperiod until the 6-month mark that is called “recent infection”. Special consideration has been given to AHI since the first US guidelines were released in 1998,[2] while “recent infection” was only added to the same epigraph in the February 2013 update, when antiretroviral treatment (ART) was already recommended for all HIV-infected individuals. The debate regarding the recommendation to start ART during “early infection” had subsequently waned, although special considerations from the 2013 update have remained in place until the most recent update. In this context, pathological data from small studies have revealed a distinct and dynamic sequence of overwhelming interactions between the HIV and the patient’s immune system, which takes place during the first few days after infection and likely influence the course of the subsequent chronic infection and its prognosis.

Therapeutic intervention at the earliest possible time may potentially affect this sequence, which is a hypothesis that is supported by additional data from other small but intensive studies.[3] Three randomized clinical trials have explored this general hypothesis in different scenarios (especially at different time-defined stages after the transmission, ranging from the protocol-specified exclusion of AHI cases in the ACTG A5217 trial, to the inclusion of a majority of AHI cases in the Primo SHM trial, or the almost exclusive inclusion of cases of recent infection in the SPARTAC) and with different outcome variables (virological in the Primo and in the ACTG trials, and immunological in the SPARTAC).[4–6] Therefore, we aimed to determine whether, in an unselected clinical setting, the early introduction of integrase strand-transfer inhibitors (ISTI) provided an easily detectable immunological benefit. This treatment has several theoretical advantages, including the
elimination of resistance testing and the rapid control of viral replication (based on reductions in the HIV viral load).

2. Methods

We reviewed the medical records of patients who attended participating clinics and fulfilled the 2 following criteria:

1. A definite or probable diagnosis of “early infection”:
   - Definite EHI based on (i) a negative serological test result during the 6 months before the diagnosis or (ii) a simultaneous negative serological test result and a positive HIV-RNA test result.
   - Probable EHI based on (i) no negative serological test result during the previous 6 months plus (ii) an epidemiological and clinical syndrome suggestive of acute HIV infection plus an HIV-RNA plasma concentration (VL) of >100,000 copies/mL.

2. Started ART using an INSTI plus 2 nucleoside analogs during the first 6 months after the diagnosis of HIV infection (based on the first positive result for anti-HIV antibodies or plasma HIV-RNA).

The outcome variables were defined as the approximately 1-year changes in the patients’ CD4+ cell count, CD8+ cell count, CD4+ percentage, and CD4+/CD8+ ratio. The baseline visit was defined as the first clinic visit and the 1-year measurement was obtained at the visit that was closest to 1 year after the baseline visit. The main explanatory variable was defined as the interval (days) between the baseline visit and the start of ART. We also evaluated the interval between the diagnosis of HIV and the start of ART. Moreover, we performed subgroup sensitivity analyses based on variables of theoretical interest (e.g., specific INSTI drugs and whether the diagnosis was definite or probable). Patients were included if they continued ART for at least 1 year, regardless of whether they were still receiving the original treatment regimen, as we aimed to evaluate the effect of the interval to the start of ART, rather than the effects of specific drugs or drug combinations on immunological recovery. All analyses involved simple linear regression analysis after determining that the dataset fulfilled the requisite conditions. However, we failed to detect significant correlations in the main and secondary analyses and elected not to perform subsequent multivariate modeling.

This study was approved by the Ethics Committee of Clinical Investigation of Cantabria.

3. Results

Fifty-three patients fulfilled the inclusion criteria between April 2014 and August 2016. The exclusions were 1 patient who was prescribed dolutegravir but decided not to take it and 3 patients who were lost to follow-up after 0 months, 2 months, and 7 months. The remaining 49 patients completed the 1-year follow-up, although only partial data were available for baseline CD4+ count (46 patients), CD8+ count (42 patients), VL (47 patients), and CD4+ percentage (48 patients). The vast majority of patients were male (48 patients, 98%). The routes of HIV transmission were needle sharing (1 patient, 2%), heterosexual relations (5 patients, 10.2%), and men who had sex with men (43 patients, 87.8%). The median age was 37 (interquartile range: 31–39). A definite diagnosis of EHI was made in 29 cases (59.2%). The treatment drugs were elvitegravir (38 patients, 77.6%), dolutegravir (9 patients, 18.4%), and raltegravir (2 patients, 4.1%). The median interval from the baseline visit to the start of ART was 12 days (interquartile range: 0–18 days), and 16 patients started ART on the day of the first visit.

Table 1 and Figure 1 show the data for the variables of interest and their scatterplots. No significant correlation with the interval to the start of ART was observed for the changes in CD4+ cell count (R = .12, P = .42), CD8+ cell count (R = .107, P = .5), CD4+ cell percentage (R = .14, P = .34), and the CD4+/CD8+ ratio (R = .23, P = .14). Furthermore, the subgroup sensitivity analyses failed to detect significant correlations for definite or probable diagnoses, treatment using elvitegravir or dolutegravir, or the time from HIV diagnosis to the start of ART. The median change in CD4+ cell count was +227/mL for patients who started ART at baseline and +343/mL for the remaining patients (P = .254, Mann–Whitney U test). Finally, we found no correlation between age and any of the 4 specified outcome variables. CD4+ counts increased by a median of 328 cells/mL in the subgroup of patients with ages above the median and by 243 cells/mL in the subgroup with ages below it (P = .45, Mann–Whitney U test).

Five patients changed their prescribed treatments during the first year of follow-up. Four patients had started receiving elvitegravir and switched treatments because of side effects (3 cases) or virologic failure (1 case). One patient had started receiving raltegravir and switched treatment based on a change in hospital policy. All 49 patients had VLs of <200 copies/mL after 1 year of treatment, including 44 patients with <20 copies/mL and 2 patients with 20–50 copies/mL.

### Table 1

|                | Baseline CD4+ count /mm³ | Baseline CD8+ count /mm³ | Baseline CD4+ percentage | Baseline log10 Viral load | Change CD4+ count /mm³ | Change CD8+ count /mm³ | Change CD4+ percentage | Change CD4+/CD8+ % |
|----------------|--------------------------|--------------------------|--------------------------|---------------------------|------------------------|------------------------|------------------------|----------------------|
| Global         | 439 (263–561)            | 981 (589–1573)           | 22 (14–25)               | 5.39 (4.48–6.05)          | 279 (134–498)          | 63 (514–329)           | 10.5 (4.0–15.0)        | .37 (0.15–0.62)       |
| Definite (n=29)| 466 (290–568)            | 944 (531–1359)           | 24 (16–27)               | 5.38 (4.93–6.34)          | 327 (200–560)          | 57 (501–322)           | 11.50 (4.75–19.00)     | .46 (2.3–69)          |
| Probable (n=20)| 377 (233–528)            | 1031 (620–1991)          | 19 (12–23)               | 5.55 (4.74–5.89)          | 254 (102–393)          | 70 (474–1338)          | 8.00 (3.00–14.00)      | .24 (0.08–40)         |
| Elvitegravir (n=38)| 454 (277–557)      | 890 (617–1626)           | 20 (14–25)               | 5.40 (4.97–5.98)          | 277 (156–333)          | 70 (324–553)           | 11.50 (4.75–14.25)     | .32 (1.4–60)          |
| Dolutegravir (n=9)| 441 (300–712)           | 1196 (399–1716)          | 24 (19–31)               | 5.20 (4.62–6.40)          | 495 (194–735)          | 5 (616–582)            | 7.00 (5.00–14.00)      | .39 (0.18–89)         |
| <500 CD4+ cells/mm³ at BL (n=29)| 336 (178–440)       | 758 (521–1353)           | 16.50                    | 5.64 (4.99–6.18)          | 257 (142–481)          | 63 (491–318)           | 12.00 (6.00–14.50)     | .34 (0.16–61)         |
| >500 CD4+ cells/mm³ at BL (n=17)| 610 (557–811)        | 1138 (623–1805)          | 26.00                    | 5.09 (4.51–6.10)          | 372 (90–575)           | 60 (l–711–572)         | 12.00 (7.00–14.00)     | 0.38 (0.06–67)        |

All values are medians and interquartile range in brackets.
4. Discussion

This series of EHI cases revealed that ART using ISTI-based regimens was efficacious, well-tolerated, and led to high levels of treatment adherence and retention. However, we did not detect any benefit from earlier treatment initiation based on improvements in the common parameters of immunological recovery. It is important to note that these patients were treated as part of standard clinical care and away from any experimental milieu.

Advances in our understanding of the unique pathogenetic events during AHI and EHI have provided strong support for the earliest possible initiation of ART. However, the available clinical evidence is less compelling, as most studies have been restricted to small heterogeneous case series that revealed very modest benefits based on second-line surrogate immunological markers and virological markers. Data from a well-characterized cohort of patients with AHI in Thailand indicates that the transition to Fiebig stages IV/V involves irreversible damage to the central immune system compartment. However, despite the detailed array of immunological and histopathological data, it is not reported whether the median CD4+ peripheral cell counts changes differed across Fiebig-stage based subgroups of patients. This is important, as the peripheral compartment retains greater capacity for recovery, based on numerous clinical trials involving patients starting ART in the chronic phase. Another well-characterized cohort of patients with AHI in San Diego has revealed that the likelihood of peripheral immunologic recovery improves when ART is started as early as possible, although the strongest driver of this recovery was the reduced immunological deterioration before the start of treatment. Based on those findings, it is unsurprising that our patients who started ART when their CD4+ cell counts were >500/mL reached even higher levels after 1 year of treatment, with a median value that was within the range defined in the San Diego study as “recovered”. However, the absolute magnitudes of the increases in CD4+ cell count, CD4+ percentage, and CD4+/CD8+ ratio were similar between our subgroups of patients with starting CD4+ cell counts of ≥500/mL and <500/mL, and the magnitude of these increases were not correlated with the intervals from the diagnosis or first visit to the start of ART.
Nevertheless, it is unrealistic to target early-stage population-wide interventions, based on the methods of the Thailand and San Diego studies, and a real-world approach must target some compromise between a highly proactive research setting and real clinical practice. The results of the randomized SPARTAC trial, which recruited EHI cases with broad time-from-infection intervals, suggest that only very modest benefits were observed in delayed immunological deterioration (the primary endpoint) among patients who were randomized <12 weeks after seroconversion. Our results do not contradict the very plausible interpretation that very early initiation of ART during AHI can have a significant beneficial effect on immunological preservation or recovery. However, based on our data from real clinical practice, it appears that physicians are not likely to encounter these patients during the “very early” window for starting ART, and that the treatment options at the initial encounter can likely be based on those for chronic infection.

Our study has some limitations derived from its retrospective nature. However, we believe that the common sources of bias in observational studies are minimal in ours and that they are unlikely to have influenced the overall conclusions. All the participating clinics share a software application for HIV clinical care (AC&H, AMVACH, Suances Spain) in which all patients been cared-for at each clinic are registered and their data prospectively recorded after their informed consent has been given. Therefore, selection and information biases should be of no concern. As for confounding, it is unlikely that an unexpected and uncontrolled variable that could have influenced the decision or time to initiate ART would have had an effect on the outcome variables selected for our study.

Author contributions

Conceptualization: Ramon Teira Cobo, Elisa Martínez, Pepa Muñoz, Belén de la Fuente, Marta Montero.
Data curation: Ramon Teira Cobo, Mar Gutierrez, Pepa Galindo, Elisa Martínez, Pepa Muñoz, Belén de la Fuente, Francisco Téllez, Marta Montero.
Formal analysis: Ramon Teira Cobo.
Investigation: Mar Gutierrez.
Methodology: Pepa Muñoz, Francisco Téllez, Marta Montero.
Project administration: Ramon Teira Cobo, Marta Montero.
Supervision: Ramon Teira Cobo, Pepa Galindo, Elisa Martínez, Pepa Muñoz, Francisco Téllez, Marta Montero.
Validation: Pepa Muñoz.
Writing – original draft: Ramon Teira Cobo.
Writing – review & editing: Ramon Teira Cobo, Mar Gutierrez, Pepa Galindo, Elisa Martínez, Pepa Muñoz, Belén de la Fuente, Francisco Téllez, Marta Montero.

References

[1] Panel on antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultAdolescentGL.pdf [access date April 23, 2018].
[2] Centers for Disease Control Prevention. Report of the NIH Panel to Define Principles of Therapy of HIV Infection and Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. MMWR, 1998; 47(No. RR-5): (1–83).
[3] Cohen MS, Shaw GM, McMichael AJ, et al. Acute HIV-1 infection. N Engl J Med 2011;364:1943–54.
[4] Hogan CM, DeGruttola V, Sun X, et al. The setpoint study (ACTG A5217): effect of immediate versus deferred antiretroviral therapy on virologic set point in recently HIV-1 infected individuals. J Infect Dis 2012;205:87–96.
[5] Grijsen ML, Steingrover R, Wit FNM, et al. No treatment versus 24 or 60 weeks of antiretroviral treatment during primary HIV infection: the randomized primo-SHM trial. PLoS Med 2012;9:e1001196.
[6] The SPARTAC trial investigatorsShort-course antiretroviral therapy in primary HIV infection. N Engl J Med 2013;368:207–17.
[7] Guadalupe M, Reay E, Sankaran S, et al. Severe CD4+ T-cell depletion in gut lymphoid tissue during primary human immunodeficiency virus type 1 infection and substantial delay in restoration following highly active antiretroviral therapy. J Virol 2003;77:11708–17.
[8] Malhotra U, Berrey MM, Huang Y, et al. Effect of combination antiretroviral therapy on T-cell immunity in acute human immunodeficiency virus type 1 infection. J Infect Dis 2000;181:121–31.
[9] Le T, Wright EJ, Smith DM, et al. Enhanced CD4+ T-cell recovery with earlier HIV-1 antiretroviral therapy. N Engl J Med 2013;368:218–30.