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Primary HIV infection: are current data definitive to treat all patients?

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ABSTRACT:

Primary HIV Infection (PHI) covers a period of 100 days. The prevalence of PHI according to Fiebig classification is low, often due to a tardive diagnosis.

Antiretroviral guidelines recommend therapy in symptomatic patients, but there are different reasons to consider treatment in asymptomatic patients as well: virological and immunological events occur during this first phase of infection; higher fraction of HIV transmission could occur in this phase; functional cure of HIV infection could be evaluated in this setting.

In this review we report the advantages of PHI treatment, we discuss different antiretroviral therapy combinations and consider perspectives for a functional cure.

Keywords: HIV, Functional cure, Primary HIV infection, Immunity, Visconti cohort.

INTRODUCTION

Primary HIV Infection (PHI) is the first stage of HIV infection, and it covers a period of 100 days. The sequential emersion of assay reactivity allows the classification of six different laboratory stages, known as Fiebig's classification[1]. There is a correspondence between stages, HIV-RNA level and symptoms: the median HIV-1-RNA levels in stage II tended to be on average 2 log10 higher than those in stage I, HIV-RNA levels are then consistent through stages II, III and IV, and a decrease in stages V and VI (Figure 1)[2]. Symptoms of acute retroviral syndrome (fever, lymphadenopathy, headache) usually appear during Fiebig II and occur for 3-10 days.

Immediately after exposure and transmission HIV-1 replicates in the mucosa, submucosa, and draining lymphoreticular tissues, establishing HIV reservoirs; within a few days, viral replication converges on the lymphoreticular system of the gastrointestinal tract (gut associated lymphoid tissue)[3].

The prevalence of PHI in new HIV diagnosis is not well known; there are some data about prevalence in special settings, in particular in sexually transmitted diseases clinics[4], 2.3% of new diagnosis with a prevalence of 1.03%; general prevalence in HIV testing was 0.3%.

Current antiretroviral (ART) guidelines recommend therapy in PHI in symptomatic patients. In this review, we will analyze benefits and doubts about starting therapy in all patients with PHI.

TREATMENT RECOMMENDATIONS

All antiretroviral guidelines[5,6,7] recommend therapy in PHI using the same parameters of chronic HIV infection. Recent published data of the START study[8] underline that early initiation of ART provides benefits in terms of AIDS and non-AIDS events. Although these concepts are clear in chronic HIV infection, guidelines underline that there are not definitive data about immunological, virological and clinical benefits in PHI. For these reasons, BHIVA guidelines[9] strictly recommend ART in PHI, only in patients with CD4<350/mmc or neurological symptoms.

The other important question is what to start: guidelines generally recommend the use of drugs with a high genetic barrier, because ART is initiated in the absence of genotypic resistance testing results.

Even if triple therapy is the first choice in PHI, with a preferred use of protease inhibitors, different studies

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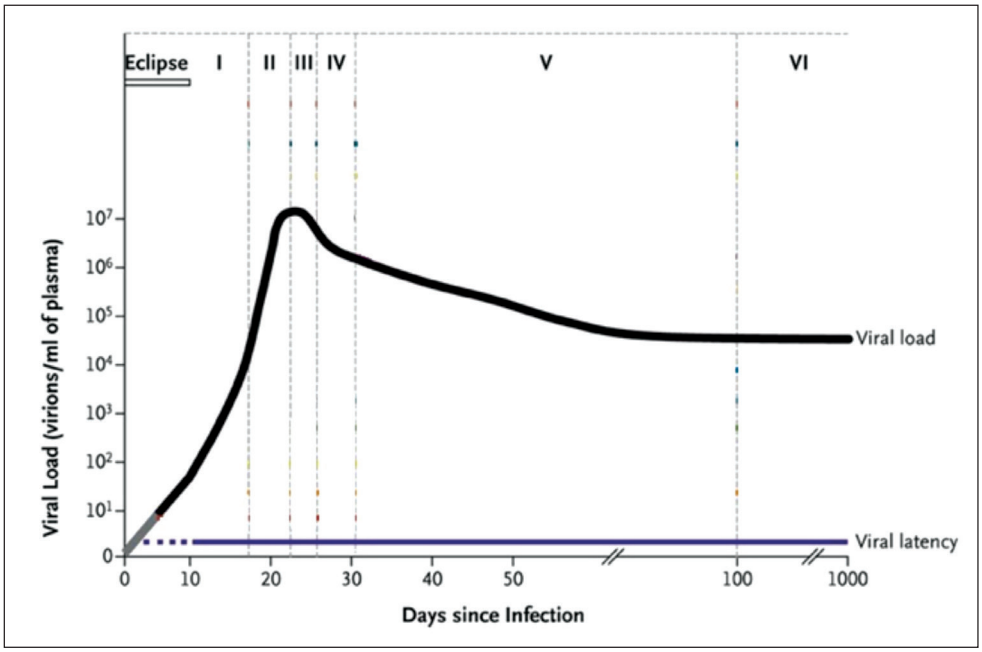

Figure 1. HIV-RNA and viral latency according to Fiebig's stages.

have associated to standard triple therapy PI/r based other drugs to reduce immune activation and/or viral reservoirs.

Antiretroviral treatment intensification

Most used drugs in this setting are CCR5 antagonist maraviroc and integrase inhibitor raltegravir.

In OPTIPRIM trial, 90 patients were randomized 1:1 to standard triple ART regimen (disoproxil fumarate 300 mg plus emtricitabine 200 mg, darunavir 800 mg,and ritonavir 100 mg once daily) or intensive five-drug ART regimen (raltegravir 400 mg and maraviroc 150 mg twice daily, and a fixed-dose combination of

tenofovir disoproxil fumarate 300 mg plus emtricitabine 200 mg, darunavir 800 mg, and ritonavir 100 mg once daily)[10]. More than 90% of patients in both groups had viral load suppression (<50 copies /mL) at month 24. A marked decline in the size of HIV blood reservoirs was reported at month 24 in both groups, without differences between the groups. Authors conclude that the continuous decline in HIV-DNA reported until month 24 suggests that a precocious and protracted effect of ART on HIV reservoirs would be beneficial for all patients whose treatment is initiated during primary HIV-1 infection.

Similar results were observed in a smaller cohort[11]: the addition of raltegravir and maraviroc to PI-based triple ART failed to show any substantial differences in the comprehensive panel of virologic and immunologic parameters measured during 96 weeks of therapy.

After 48 weeks of four intensive ART drugs containing maraviroc, we documented a reduction in activated B cells and CD8(+) T cells. Natural killer cell and dendritic cell frequencies were measured and a decrease in CD16(+) CD56(dim) with a reciprocal rise in CD56(high) natural killer cells and an increase in myeloid and plasmacytoid dendritic cells were recorded. In conclusion, 48 weeks of cART during PHI showed significant benefits for both innate and adaptive immunity[12].

Use of immunomodulating agents

During PHI, T cell activation is observed during the first phase of infection. The use of immunomodulating agents could lessen this phenomenon. Certain clinical immunosuppressants and chemotherapeutic agents may act combinatorially to inhibit HIV infection. In particular mycophenolic acid and cyclosporine[13,14], and the chemotherapeutic, cytarabine, are potent antiretroviral agents at clinically relevant dosages. These drugs strongly inhibit HIV-1 replication in a GFP indicator T cell line and peripheral blood mononuclear cells (PBMC).

Although there are not in vivo studies with these agents, the available in vitro studies and the demonstrated mechanism of action could support the use in PHI.

The use of HIV therapeutic vaccines against HIV epitopes could amplify the immunological response in a large proportion of patients during PHI. To test this hypothesis, PRIMOVAC-ANRS 095 Study, a prospective randomized trial, tested two immunotherapeutic approaches, IL-2 alone and sequential immunizations with two vaccines, recombinant ALVAC-HIV (vCP1433) and HIV-1 lipopeptides Lipo-6T followed by IL-2 injections, compared with no immune intervention, in patients first treated during PHI and who had sustained viral control[15]. HIV-specific CD4 T cell responses did not change during the study period in immunized patients relative to controls, and vaccination had only a transient effect on interferon--producing CD8 responses. Viral rebound after treatment interruption was similar in immunized patients and controls.

Action on reservoirs

In 2010, it was reported that some individuals, originally treated during PHI, were capable of maintaining HIV Viral Load undetectable for several years after the interruption of ART. This cohort of "post-treatment controllers (PTC)", known as the Visconti cohort[16], has been closely characterized.

The 14 PTCs presented in this study maintained lasting control of viremia after the interruption of prolonged therapy that began early during PHI. They did not carry a favorable HLA genotype, as noted in some Elite controllers, and they are characterized by low level of HIVDNA.

Moreover, a single clinical case of the literature, know as the Mississippi baby, supported the importance of early treatment for functional HIV cure[17]: a 30-month-old child who met the standard diagnostic criteria for HIV-1 infection, received combination ART between 30 hours and 18 months of age, and subsequently had controlled HIV-1 viremia for 12 months while not receiving ART. The absence of rebound viremia, the undetectable replication-competent virus, the almost-complete disappearance of cell-associated HIV-1 DNA, and the absence of HIV-1–specific immune responses while the child was not receiving ART suggest that replication-competent HIV-1 reservoirs may not have been established.

Conclusions

Treatment initiation during primary HIV-1 infection (PHI) seems to be critical, related to the time of infection and it is not different with different ART combination. Furthermore, early treatment preserves innate immunity and T and B cell functions, thus accelerating immune restoration.

PRIMOVAC, the VISCONTI Cohort and the Mississippi baby data suggest that very early ART may positively interfere with the quantities and/or qualities of persistent reservoirs and replication-competent virus. Moreover, viral rebound occurs later and at a lower level after the discontinuation of treatment that began during PHI. Actual data underline that treatment during PHI is the unique demonstrated possibility of a functional cure.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

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