

2016

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Recommended Citation

Winkler ML. Early HAART should be used for treatment-naive HIV patients with Pneumocystis pneumonia. *Clin. Res. Pract.* 2016 Aug 26;2(2):eP1105. doi: [10.22237/crp/1472227845](https://doi.org/10.22237/crp/1472227845)

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Early HAART should be used for treatment-naïve HIV patients with *Pneumocystis pneumonia*

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ABSTRACT A critical appraisal and clinical application of Manzardo C, Esteve A, Ortega N, et al. Optimal timing for initiation of highly active antiretroviral therapy in treatment-naïve human immunodeficiency virus-1-infected individuals presenting with AIDS-defining diseases: the experience of the PISCIS Cohort. *Clin. Microbiol. Infect.* 2013 July;19(7):646-653. doi: [10.1111/j.1469-0691.2012.03991.x](https://doi.org/10.1111/j.1469-0691.2012.03991.x)

Keywords: HAART, PCP, pneumocystis, HIV, initiation of therapy, initiation of HAART, timing of HAART

Clinical Context

The patient is a 32-year-old male being seen in the clinic. About six weeks before this visit, he was admitted directly to the hospital for desaturating to 68% SaO₂ while ambulating in the Infectious Disease clinic. He was seen there for a two-month history of diarrhea and progressive cough with dyspnea on exertion, and a positive home Human Immunodeficiency Virus (HIV) test that he took five days before presenting at the ID clinic. Blood tests from the clinic revealed that his CD-4 count was 27 cells/mL with a viral load of 194,000 IU/mL, and a viral genotype was sent out. He was begun on treatment for *Pneumocystis jirovecii* pneumonia (PCP) presumptively, while confirmatory lab results were pending. Highly active anti-retroviral therapy (HAART) was not initiated in the hospital, with a planned start once the viral genotype returned to determine treatment susceptibility. This follow-up visit at the HIV clinic was arranged prior to hospital discharge.

Clinical Question

What is the optimal time to initiate HAART in a treatment-naïve HIV patient with *Pneumocystis pneumonia*?

Research Article

Manzardo C, Esteve A, Ortega N, et al. Optimal timing for initiation of highly active antiretroviral therapy in treatment-naïve human immunodeficiency virus-1-infected individuals presenting with AIDS-defining diseases: the experience of the PISCIS Cohort. *Clin. Microbiol. Infect.* 2013 July;19(7):646-653. doi: [10.1111/j.1469-0691.2012.03991.x](https://doi.org/10.1111/j.1469-0691.2012.03991.x)

Literature Review

A PubMed search was performed with MeSH terms “Antiretroviral Therapy, Highly Active,” “*Pneumocystis jirovecii*,” and “AIDS-related opportunistic infections,” which initially returned many studies focused on tuberculosis as the opportunistic infection (OI).

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ISSN: 2379-4550

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However, a study which concerned early-initiation of HAART in patients with opportunistic infections was found¹ that examined the application of the AIDS Clinical Trials Group (ACTG) A5164 trial² to patients with *Pneumocystis pneumonia*. After reviewing references from this paper, two studies investigating HAART therapy timing after opportunistic infections were found^{2,3}, along with a non-systematic review of six randomized controlled trials and several observational studies⁴.

The meta-analysis by Lawn, et al.⁴ was not appropriate for review due to the fact that many of the studies analyzed were from resource-poor countries, and many of these studies focused on tuberculosis as the primary opportunistic infection. The landmark A5164 study, a prospective RCT of early HAART in newly diagnosed AIDS patients with opportunistic infections, by Zolopa, et al.² was an open-label, randomized, controlled trial of 282 patients. Patients were randomized to either early or deferred initiation of HAART. Their results showed a statistically significant decrease in death and progression to AIDS in patients in the early initiation arm. Unfortunately, many of the patients enrolled had multiple opportunistic infections, and/or had previously received HAART. These were felt to be a significant deviation from our patient, and so the study was not selected for appraisal. Ultimately the Manzano, et al., cohort study³ was selected for appraisal, having the highest number of patients with PCP as the opportunistic infection, being from a country with a high level of care, and having patient characteristics most similar to our patient including first AIDS diagnosis, treatment-naïve, and low CD4 count.

Critical Appraisal

This was a prospective cohort study using subjects from the PISCIS cohort, comprised of newly attending HIV-infected patients aged 16 and older from ten hospitals in Spain; inclusion criteria were first acquired immunodeficiency syndrome (AIDS) diagnosis, treatment-naïve, available CD4 count, and follow-up >30 days. Patients were excluded if they had a first diagnosis of HIV encephalopathy, interstitial lymphoid pneumonia, HIV-associated wasting syndrome, or did not initiate HAART within the specified time frames. Notably, patients who did not initiate HAART but died within the first 30 days were not included in the study. The early treatment group (277, of which 94 had PCP) consisted of patients who started HAART within 30 days of AIDS diagnosis, and the late treatment group (348, including 101 with PCP) initiated HAART 30-270 days after AIDS diagnosis. The initiation of HAART was determined by the physicians, with outcomes analyzed *a posteriori*. Outcomes analyzed were mortality, and a combined endpoint of progression to AIDS/death. Progression to AIDS/death included contracting a second AIDS-defining condition such as PCP or Kaposi Sarcoma after treatment of the first, original opportunistic infection. For the subgroup of patients with PCP, early initiation of HAART was clearly beneficial, with a 2.1% mortality vs 15.8% in late starters ($p < 0.001$) and progression to AIDS/death was 16% vs 30.7% ($p = 0.015$).

This was a well-designed study with clear, valid inclusion and exclusion criteria and high levels of follow-up at over 80%. The exclusion criteria of failure to initiate HAART within the study timeframe may have introduced bias, for several reasons. If these 108 patients were well enough or poor enough that their clinicians decided to not initiate HAART early, their inclusion in the 'late' arm may have biased the group towards either lower or higher mortality. Another reason is described by the authors: "In most cases, the reason for never starting or delaying HAART was loss to follow-up, especially in immigrants and active injecting drug users." The fact that injection drug users were preferentially lost to follow-up is a large source of bias, since this will skew group demographics and make the study less applicable to the overall population with HIV and an opportunistic infection.

Since it is a prospective cohort, there was no randomization or matching between groups, though the authors state that their demographic characteristics were "broadly similar." However, the observational nature of the study is still a significant source of potential bias. Upon examination of the patient demographics, there was no specific breakdown by opportunistic infection, but the categories with significant differences between early and late HAART were Transmission Group (higher percentage of IV drug users and lower percentage of homosexual/bisexuals in the deferred HAART group), CD4 count (deferred was higher), Hepatitis C co-infection (deferred was higher). They are indeed broadly similar, but these differences may have contributed to the significance of the study results. For one, continued intravenous drug use is an independent risk factor for morbidity and mortality, creating a confounding factor for the higher mortality in the deferred HAART group. Hepatitis C is also a strong comorbidity that could account for higher mortality in the deferred group. Furthermore, delaying HAART due to higher CD4 counts has been proposed as the standard of care. This all contributes to the clinical decision on when to initiate HAART. It seems likely that cultural bias and entrenched treatment algorithms contributed to this decision, which created significant differences between the groups, which in turn may have falsely created the mortality difference. The authors do acknowledge that this clinical decision may have introduced bias, but they dismissed this conclusion without much examination. There were also differences in the AIDS-defining condition



between early and late treatment groups; however, 33.9% of early-initiators had PCP and 29% of late-initiators had PCP so this should not introduce a significant bias. Additionally, immunologic and virologic response to HAART was not significantly different between groups, removing this as a source of confounding.

An important factor to consider when initiating HAART during an opportunistic infection is Immune Reconstitution Inflammatory Syndrome (IRIS), which was not recorded in this study. This was a serious flaw, but the authors again dismiss this by stating that overall mortality was no greater in patients in the early HAART arm, which suggests that IRIS has little mortality effect in early initiation of HAART. They also state that IRIS has a much stronger association with tuberculosis than other opportunistic infections, but fail to cite a reference for this fact.

According to the Oxford Centre for Evidence-Based Medicine criteria, the level of evidence is 2b for this cohort study. The control group was late-starters of HAART, and if the mortality outcome in patients with PCP is used, an absolute risk reduction (ARR) of 13.7% and a calculated number needed to treat (NNT) of 7.3 patients is evident, although the authors did not report ARR or NNT. For progression to AIDS the ARR was 14.7% with a NNT of 6.8 patients. Using crude mortality data in Table S1³, the number needed to harm for delaying HAART therapy more than thirty days for treatment-naïve HIV positive patients for death is 13.7 over a period of twelve months. These data are less reliable, as this was a cohort study and not a randomized controlled trial, but their results are similar to the results from study group A1546, which was a randomized controlled trial. This is a strong indicator that early HAART is beneficial to AIDS patients with PCP, and that deferring treatment can cause harm.

Clinical Application

This cohort study suggests a mortality benefit and an HIV-disease progression benefit to initiating HAART within thirty days of diagnosis of PCP in a treatment-naïve patient such as ours. Along with the results from the A5164 randomized trial, we believe there is mortality benefit to initiating HAART early in patients with HIV, even when they have opportunistic infections. Based on this evidence, the patient was started on HAART immediately.

Take Home Points:

- 1.) Delaying HAART therapy in HIV patients with opportunistic infection increases mortality.
- 2.) Since delaying treatment causes harm, it is important to ensure appropriate follow-up to prevent delay.
- 3.) Fears about IRIS due to HAART therapy are not rooted in scientific evidence. Even if IRIS is a concern, the potential harms due to IRIS are outweighed by the potential benefits of early improved HIV control.

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