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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Is early antiretroviral therapy initiation useful in HIV(+) adults without co-infections?

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Abstract

HIV infection is a worldwide epidemic. Antiretroviral therapy has dramatically changed the outcome of the disease but there is still controversy about the best time to initiate it, especially in patients with CD4 counts over 350 cells/µL. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified two systematic reviews including four pertinent randomized controlled trials overall. We concluded early initiation of antiretroviral therapy probably reduces mortality, risk of opportunistic infections and tuberculosis, but increases the risk of important adverse effects.

Problem

Human immunodeficiency virus (HIV) infection is a worldwide epidemic. The use of antiretroviral therapy has changed the outcome of the disease, clearly and consistently reducing mortality. There is wide agreement about the benefits of starting antiretroviral therapy in patients at B or C stage, CD4 count below 350, during pregnancy or lactation, in patients co-infected with hepatitis C virus, hepatitis B virus or tuberculosis, HCV, and in patients over 50 years of age. However, there is no consensus about the effects of early initiation of antiretroviral therapy in patients with CD4 counts over 350.

Methods

We used Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this information, we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages
- Early initiation of antiretroviral therapy probably reduces the risk of mortality, opportunistic diseases and tuberculosis in HIV(+) adults
- Early use of antiretroviral therapy probably increases the risk of grade 3 and 4 laboratory adverse effects.
- Existing systematic reviews do not include a recently published randomized study that could increase the certainty of the evidence.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found two systematic reviews [1],[2], that consider 23 primary studies reported in 25 references [3],[4],[5],[6],[7],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27], including four randomized controlled trials reported in six references [6],[11],[12],[13],[16],[20]. This table and the summary in general are based on the latter.
What types of patients were included	Two studies were conducted in multiple countries [6],[11], one in Haiti [13] and one in the USA [16]. All of the studies included patients over 18 years of age, except one study that included younger patients (over 13 years)[11]. All studies included HIV infected adults, naïve to treatment and willing to be treated. One study included patients with CD4 counts equal or greater than 350 [11], one with CD4 counts between 200 and 350 [13], one with CD4 counts between 350 and 500 [6] and other with CD4 counts equal or greater than 350 [16]. Average of CD4 counts across studies was 337. All studies excluded pregnant or nursing women, patients in advanced stage of disease (AIDS) or with previous use of antiretroviral therapy. Two studies included normal laboratory parameters among their inclusion criteria [6],[16].
What types of interventions were included	The interventions were: • Viral suppression strategy (uninterrupted use of antiretroviral therapy for maximal viral suppression) versus drug maintenance strategy (sporadic use of antiretroviral therapy with subgroups for early [greater than 350 CD4] and standard antiretroviral initiation) [11]. • Deferred initiation (CD4 less than 200 or AIDS) versus early initiation two weeks after enrollment [13]. • Antiretroviral therapy initiation with ABC/3TC versus TDF/FTC in patients with CD4 counts greater than 350[16]. • Deferred initiation of antiretroviral therapy (CD4 counts below 250 or AIDS) versus early initiation with CD4 counts between 350 and 550 and serodiscordant couples [6].
What types of outcomes were measured	The following outcomes were measured: • Death • Opportunistic diseases • AIDS related events • Grade 3-4 adverse events • Incidence of tuberculosis • Adverse events not related to AIDS • Virologic failure • AIDS free couple for 6 months

Summary of findings

The information on the effects of early initiation of antiretroviral therapy in HIV infected patients with CD4 counts over 350 is based on four randomized controlled trials [6],[11],[13],[16], that include 4,686 patients. Two studies [6],[11], measured the outcome opportunistic infections, three [6],[11],[13] the outcome tuberculosis, three [6],[11],[13] measured mortality and two studies [6],[13] measured grade 3-4 adverse events.

- Early initiation of antiretroviral therapy probably reduces the incidence of opportunistic diseases. The certainty of the evidence is moderate.
- Early initiation of antiretroviral therapy probably reduces the incidence of tuberculosis. The certainty of the evidence is moderate.
- Early initiation of antiretroviral therapy probably reduces mortality in HIV infected patients. The certainty of the evidence is moderate.
- Early initiation of antiretroviral therapy probably increases the risk of grade 3-4 adverse events. The certainty of the evidence is moderate.

Early antiretroviral therapy initiation in HIV(+) patients without co-infections.

Patients HIV(+) naïve to treatment, without co-infections.
Intervention Early highly active antiretroviral therapy (HAART) (CD4 count 350 or more)
Comparison Standard HAART

Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT early HAART	**WITH early HAART**		
	Difference: patients per 1000			
Opportunistic disease	40 per 1000	23 per 1000	RR 0.59 (0.38 to 0.92)	⊕⊕⊕◯[1,2] Moderate
	Difference: 17 patients less per 1000 (Margin of error: 3 to 24 less)			
Tuberculosis	18 per 1000	11 per 1000	RR 0.63 (0.41 to 0.97)	⊕⊕⊕◯[1,2] Moderate
	Difference: 7 patients less per 1000 (Margin of error: 1 to 11 less)			
Mortality	26 per 1000	12 per 1000	RR 0.44 (0.25 to 0.77)	⊕⊕⊕◯[1,2] Moderate
	Difference: 14 patients less per 1000 (Margin of error: 6 to 20 less)			
Adverse effects grade 3 or 4	107 per 1000	122 per 1000	RR 1.14 (0.92 to 1.42)	⊕⊕⊕◯[3] Moderate
	Difference: 15 patients more per 1000 (Margin of error: 9 less to 45 more)			

RR: Risk ratio.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

* The risk **WITHOUT early HAART** is based on the risk in the control group of the trials. The risk **WITH early HAART** (and its margin of error) is calculated from relative effect (and its margin of error).

1 The certainty of the evidence was downgraded because of high risk of bias of primary studies; since randomized studies were not blinded.
2 We did not decrease the certainty of evidence for imprecision even though the margin of the confidence interval includes the possibility of the effect being small and not clinically relevant. However, there is agreement in the direction of the outcomes, which are causally connected.
3 Certainty of evidence has been reduced because of imprecision.

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

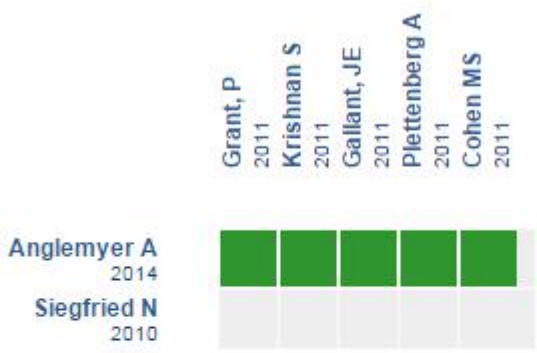
*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply
• This evidence applies to all HIV infected patients naïve to treatment with antiretroviral therapy. • This evidence does not apply to pregnant women, nursing women, patients with AIDS, HIV kidney disease or neuropathy, because in these cases, early antiretroviral therapy is mandatory regardless of CD4 counts.
About the outcomes included in this summary
• We selected outcomes critical for decision-making according to the opinion of the authors of this summary.
Balance between benefits and risks, and certainty of the evidence
• Regarding the balance between risks and benefits, there is a probable benefit of the intervention in terms of mortality, opportunistic infections and tuberculosis, which despite a greater risk of adverse events inclines the balance in favor of early antiretroviral therapy. It is important to have in mind the certainty of the evidence is moderate. • The evidence of observational studies also reinforces the conclusion of this summary: a collaborative analysis of 18 prospective cohorts [28] of HIV infected patients naïve to treatment, suggests similar conclusions, and emphasizes deferred antiretroviral therapy is associated with increased risk of mortality and AIDS.
Resource considerations
• Although costs of antiretroviral therapy are high, it is very likely that benefits are greater than costs. This may change depending on the different clinical scenarios and health care systems.
Differences between this summary and other sources
• Our conclusions agree with those of the systematic reviews identified in this summary. One of the reviews [2] concluded initiation of antiretroviral therapy with CD4 counts between 350 and 500 could be superior to treatment below 350. The Cochrane review [1] concludes initiation of antiretroviral therapy above 250 might reduce mortality, so it should be considered case by case. • In comparison with major clinical guidelines, our conclusions agree but have slight differences: For instance, American guidelines [29] recommend initiation of antiretroviral therapy in all patients with CD4 counts below 350, suggest it between 350 and 500, and leave it to the clinician's decision in patients with CD4 counts above 500. British guidelines [30] recommend initiation of antiretroviral therapy in every HIV infected patient.
Could this evidence change in the future?
• The probability that future evidence changes what we know is low, because of the certainty of the existing evidence. • There is a recently published randomized controlled trial (of the INSIGHT START study group) [31] in which they started antiretroviral therapy in HIV infected patients with CD4 counts over 500 versus initiation below 350 or AIDS. The inclusion of this study in future systematic reviews would increase the certainty of the evidence for this question.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version:** Early initiation of antiretroviral therapy in HIV-infected adults without coinfection

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

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