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Could Early Antiretroviral Therapy Entail More Risks than Benefits in sub-Saharan African HIV-Infected Adults? A Model-Based Analysis

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Abstract

Background—Initiation of antiretroviral therapy (ART) in all HIV-infected adults, regardless of count, is a proposed strategy for reducing HIV transmission. We investigated the conditions under which starting ART early could entail more risks than benefits for patients with high CD4 counts.

Methods—We used a simulation model to compare ART initiation upon entry to care (“immediate ART”) to initiation at CD4 350 cells/ μ L (“WHO 2010 ART”) in African adults with CD4 counts >500 cells/ μ L. We varied inputs to determine the combination of parameters (population characteristics, conditions of care, treatment outcomes) that would result in higher 15-year mortality with immediate ART.

Results—Fifteen-year mortality was 56.7% for WHO 2010 and 51.8% for immediate ART. In one-way sensitivity analysis, lower 15-year mortality was consistently achieved with immediate ART unless the rate of fatal ART toxicity was >1.0/100PY, the rate of withdrawal from care was >1.2-fold higher or the rate of ART failure due to poor adherence was >4.3-fold higher on immediate ART. In multi-way sensitivity analysis, immediate ART led to higher mortality when moderate rates of fatal ART toxicity (0.25/100PY) were combined with rates of withdrawal from care >1.1-fold higher and rates of treatment failure >2.1-fold higher on immediate ART than on WHO 2010 ART.

Conclusions—In sub-Saharan Africa, ART initiation at entry into care would improve long-term survival of patients with high CD4 counts, unless it is associated with increased withdrawal

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from care and decreased adherence. In early ART trials, a focus on retention and adherence will be critical.

Introduction

Since December 2009, the World Health Organization (WHO) has recommended that antiretroviral therapy (ART) should be started in all HIV-infected adults with CD4 counts ≥ 350 cells/ μ L.¹

In addition to guidelines recommending earlier ART initiation for individual benefit, universal testing with immediate initiation of ART upon diagnosis (“test and treat”) has been proposed as a research strategy to reduce HIV transmission by lowering the population viral load.²⁻⁴

In an ideal scenario, the test and treat approach would benefit both the population and the individual patients. At the individual level, substantial rates of non-infectious, non-AIDS morbidity (e.g., renal, cardiovascular, and oncologic diseases) are more frequent in HIV-infected adults at early stages of immunosuppression than in the general population.⁵ Starting ART earlier than is currently recommended may prevent these early non-infectious co-morbidities.⁵⁻⁸ Furthermore, high rates of early infectious morbidity, particularly of tuberculosis and invasive bacterial diseases, in patients in resource-limited settings not receiving ART suggest that early ART would be particularly beneficial to individuals without substantial immunosuppression in these settings.^{3,9-12}

However, potential patient-level risks associated with earlier initiation of ART – including increased rates of drug toxicity, decreased adherence over time, increased rates of withdrawal from care **and exhaustion of future treatment options** – could undermine the benefits to both the individual and the population.¹³ As a result, the net benefit of early ART is still unknown, and there is no certainty that the benefits/risks ratio would be the same in the short-term and in the long-term.

Several clinical trials designed to evaluate the population-level impact (i.e. the impact on HIV incidence) of a test and treat strategy are currently being discussed. In these trials, patients currently not recommended by the WHO to start ART for their own benefit will be enrolled, in order to examine the potential population-level benefits. Meanwhile, other randomized clinical trials designed to evaluate the individual-level impact (i.e. the impact on individual morbidity and mortality) of starting ART earlier than currently recommended are enrolling.¹⁴⁻¹⁶ These trials will have limited follow-up time, and their results will not be known for several years. In the meantime, mathematical models of the risks and benefits of early ART can help refine current questions and anticipate future issues by **identifying parameters likely to influence the long-term risks and benefits**.

We used a widely-published simulation model of HIV disease to assess the potential long-term risks and benefits to individuals who initiate ART very early (**500 CD4 cells/ μ L, regardless of WHO stage**) compared to the current WHO-recommended guidelines.

Methods

Analytic overview

We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)-International model¹⁶⁻¹⁸ to answer the following questions:

- i. What are the likely long-term, patient-level benefits associated with immediate ART initiation?

- ii. What are the key parameter values that could make immediate ART more harmful than beneficial to these patients?

To address the first question, we compared projected 15-year cumulative mortality in patients with CD4 counts greater than 500 cells/ μ L at first contact, according to two strategies of ART initiation: immediate ART and ART initiation following 2010 WHO recommendations. To address the second question, we conducted extensive sensitivity analyses to identify the combinations of parameters that would lead to higher 15-year cumulative mortality in the immediate ART strategy relative to ART initiation recommended by the WHO.

Strategies for ART Initiation

We compared two ART initiation strategies in a patient population based in Côte d'Ivoire that entered care with a CD4 count greater than 500 cells/ μ L: (i) immediate ART, and (ii) ART initiation at CD4 $\geq$ 350 cells/ μ L or WHO clinical stage III or IV ("WHO 2010 ART" guidelines, the new recommended standard of care in resource-limited settings).¹

To contrast this with past standards of care, we included two additional strategies in the base case: (iii) no ART, for comparison only, and (iv) ART initiation at WHO clinical stage IV, at CD4 $\geq$ 200 cells/ μ L, or at CD4 from 200-350 cells/ μ L with WHO clinical stage III ("WHO 2006 guidelines").¹⁹ These two additional strategies were not included in the sensitivity analyses.

Outcomes

The study population consisted of all HIV-infected adults who **enter care with a CD4 count greater than 500 cells/ μ L in Côte d'Ivoire**. The primary outcome was cumulative mortality 15 years after first contact with care, **expressed as the percentage of adults who died (%dead) among those who entered care with a CD4 count greater than 500 cells/ μ L**. The difference in mortality between WHO 2010 ART and immediate ART strategies was expressed as an absolute difference (%dead with WHO 2010 ART - %dead with immediate ART) and as a relative percent difference (1-[%dead with immediate ART/%dead with WHO 2010 ART]). Secondary outcomes included CD4 count change over time and cumulative risks of tuberculosis, severe bacterial diseases and other WHO stage III-IV diseases.

Analytic steps

The analysis consisted of **three** stages.

The first stage **was the** base case analysis, **in which** we reported primary and secondary outcomes using standard inputs and assumptions as defined above.

The second stage **was the one-way** sensitivity analysis, to address **the following** questions: 'What is the impact of wide variations in individual input parameters on the difference in 15-year mortality between the immediate ART and WHO 2010 ART strategies?' To answer this question, we varied inputs individually over a range of plausible values. The inputs varied included: (i) baseline CD4 count and age distributions, CD4-specific morbidity/mortality rates (**including similar variation in CD4-specific rates in patients on ART and off ART, and lower rates in patients on ART = 'ART effect'**); (ii) frequency of CD4 count and clinical monitoring; (iii) ART switching criteria (**including different definitions of immunological failure when viral load is unavailable, and different monitoring procedures and definitions of virologic failure when viral load is available**); (iv) number of available ART regimens (**one to three lines**); (v) probability of **6-month** HIV RNA

suppression on ART and virologic failure after 6 months (assuming similar probabilities with first-line and second line, and then lower 6-month HIV RNA suppression and higher virologic failure in second-line compared to first-line); (vi) CD4 count gain associated with suppressive ART (from 0 to 6 months, 6 months to 5 years, and >5 years); (vii) maximum duration of HIV RNA suppression on ART, maximum duration of CD4 count gain on ART, maximum obtainable CD4 count ('CD4 ceiling'), withdrawal rates (0 to 12 months, >12 months); (viii) probability of withdrawn patients returning to care upon the occurrence of a severe HIV-related opportunistic disease; and (ix) ART-related fatal toxicity rates. **We first varied all these parameters equally in all strategies,** and then assumed that the risk of withdrawal from care and/or that the probability of late virologic failure were higher in the immediate ART strategy than in the WHO 2010 ART strategy, due to lower rates of adherence in patients starting ART early.

The third stage was the multi-way sensitivity analysis, to address the following questions: 'Could some key input parameter values or combination of values lead to greater 15-year mortality in the immediate ART strategy than in the WHO 2010 ART strategy?' To answer this question, we varied the key determinants identified in one-way sensitivity analysis to examine the difference in mortality between the immediate ART and WHO 2010 ART strategies in multi-way sensitivity analysis.

Data inputs

We used standard model input data for the natural history of HIV disease and ART efficacy in Côte d'Ivoire.^{20,21} When different data were available in the literature for the same parameter, or when data were not available, we made assumptions meant to be neutral or to bias any results away from favoring immediate ART (conservative approach, Table 1).

The base case distributions of age, sex, and initial CD4 count were derived from the Trivacan ANRS 1269 trial and the IeDEA Côte d'Ivoire database using data for patients with a CD4 count greater than 500 cells/ μ L at first contact with a care center.^{22,23} The HIV RNA set point distribution was from the Primo-CI ANRS 1220 seroconverters cohort.^{22,23} The CD4-stratified incidence of HIV-related diseases and mortality in the absence of ART and the direct effect of ART on morbidity and mortality were from the Primo-CI ANRS 1220 and Cotrame ANRS 1203 cohorts.¹⁰ The efficacy of cotrimoxazole prophylaxis was from the ANRS 059 Cotrimo-CI trial.^{18,24} Non-HIV-related mortality, adjusted for age and gender, was derived from WHO life tables for Côte d'Ivoire.²⁵ Outcomes on ART, including 6-month plasma HIV-1 RNA suppression and CD4 increase over time, were from the Aconda program, a large PEPFAR-funded program of access to HIV care and treatment in Côte d'Ivoire.^{26,27}

ART-related fatal toxicity was defined as the probability of dying from an ART-related side effect such as cardiovascular, renal, hepatic or immuno-allergic adverse events. To the best of our knowledge, there is currently no such overall probability reported in the literature. Thus, we set the rate of ART-related fatal toxicity to zero in the base case analysis, and then varied it widely in sensitivity analysis.

Withdrawal from care was defined as a temporary or permanent interruption in HIV care and treatment. We assumed withdrawal could only occur among patients on ART – a conservative assumption with regard to the benefits of immediate therapy. The base case withdrawal rates were from the Aconda program, estimated at 11.6 per 100 person-years in the first twelve months on ART and at 9.2 per 100 person-years thereafter.²⁶

In the base case analysis, we assumed that: (i) there were only two lines of ART available, and 2nd-line ART had the same efficacy as 1st-line ART; (ii) CD4 count was measured

every six months for patients off ART and on ART, and HIV RNA tests were not available; (iii) the criteria for switching from 1st-line to 2nd-line ART were consistent with those recommended by the WHO for settings where HIV RNA monitoring is not available (a 50% decrease from peak CD4 count, a return to CD4 count nadir, a CD4 count < 100 cells/ μ L, or the occurrence of a WHO stage III or IV disease after at least 12 months on ART);¹⁹ (iv) increases in CD4 count on suppressive ART continued for 5 years or until current CD4 count reached a maximum of 1200 cells/ μ L, whichever came first;^{28,29} (v) non-fatal ART-related severe toxicity resulted in a drug substitution from the same drug class with no impact on ART failure rates or survival; (vi) patients who withdrew from care while on ART had a 50% probability of returning to care upon the occurrence of a severe HIV-related disease; (vii) all patients with a CD4 count < 500 cells/ μ L were given cotrimoxazole prophylaxis, whether off ART or on ART.³⁰ No other prophylaxis was provided; (viii) the rate of fatal toxicity was constant over time; and (ix) the withdrawal rates were the same in the immediate ART and WHO 2010 ART strategies.

CEPAC-International model

The CEPAC-International model is a Monte Carlo, state-transition simulation model of HIV disease and treatment. Details of the model structure and default input values for Côte d'Ivoire analysis have been previously described (Appendix 1 and 2).¹⁶⁻¹⁸ In summary, the model tracks the clinical course of simulated HIV-infected patients on a monthly basis from the time of entry into the model until death. In the absence of successful ART, patients' CD4 counts decline at a rate determined by their HIV RNA level.³¹ Current CD4 count determines the risk of developing an HIV-related disease or dying from HIV infection.¹⁰ The timing of ART initiation is user-specified and based on current CD4 count and/or WHO clinical stage. ART decreases morbidity and mortality indirectly by means of HIV RNA suppression and CD4 count increase, and directly by reduction in the incidence of HIV-related morbidity.³²⁻³⁴ Upon ART initiation, patients have a regimen-specific early probability of HIV RNA suppression and an associated increase in CD4 count. With suppressive ART, they have a later monthly risk of virologic ART failure (related to poor adherence and/or resistance). Switching from first-line to further lines of ART may be determined by clinical, immunologic or virologic criteria, or a combination thereof.¹⁹ When the ART switching criteria are met, a patient switches to the next sequential ART regimen until all defined sequential regimen options are exhausted. Monitoring can be clinical only (visits), or clinical with CD4 tests and/or HIV RNA tests. At any time, a patient in the model may withdraw from care, at a rate defined by the user. Such patients receive no opportunistic disease prophylaxis or ART. Should they have been on suppressive ART at the time of withdrawal, their HIV RNA returns to set point and their CD4 count rapidly declines to their pre-treatment nadir.^{9,35} Those patients may return to care upon the occurrence of a severe HIV-related opportunistic disease.

Results

Base case

The projected cumulative 15-year mortality in the No ART comparison strategy was 97.6%. This decreased to 65.2% with the WHO 2006 standard of care comparison strategy, to 56.7% with the WHO 2010 current standard of care strategy, and to 51.8% with Immediate ART (Figure 1A). Corresponding probabilities of severe morbidity are shown in Appendix 3. As shown in Figure 1, the %dead at 5 years was 10.6% with WHO 2010 ART, and 6.3% with immediate ART (absolute difference of -4.3%, relative percent difference of -40.2%); the %dead at 10 years was 31.0% with WHO 2010 ART and 25.4% with immediate ART (absolute difference of -5.6%, relative percent difference of -18.0%); and the %dead at 15

years was 56.7% with WHO 2010 ART and 51.8% with immediate ART (absolute difference of -4.9%, relative percent difference of -8.6%).

At the end of the fifteenth year of follow-up, the mean CD4 count in patients alive was estimated at 439 cells/ μ L in patients on immediate ART and 369 cells/ μ L in patients on WHO 2010 ART, as compared to 318 cells/ μ L in patients on WHO 2006 ART and 75 cells/ μ L in patients not on ART (Figure 1B).

One-way sensitivity analysis

Table 2 shows a selection of one-way sensitivity analyses where **15-year mortality remained lower with immediate ART as compared to WHO 2010 ART**. The following parameter changes resulted in an increase in the projected cumulative 15-year mortality in both strategies: (i) increasing acute mortality from severe opportunistic diseases, (ii) setting the direct effect of ART on morbidity and mortality to zero, (iii) assuming only one line of ART was available, (iv) decreasing the CD4 gain on ART, (v) decreasing 6-month viral suppression on ART in similar proportion in both strategies, (vi) increasing the rate of ART failure after 6 months in similar proportion in both strategies, (vii) increasing the rate of withdrawal from care in similar proportion in both strategies, (viii) decreasing the probability of returning to care, **and (ix) assuming lower rates of 6-month virologic suppression with second-line ART compared to first-line**. Conversely, the following parameter changes decreased projected cumulative 15-year mortality in both strategies: (i) assuming a lower mean age or a higher CD4 count at first contact, (ii) making a 3rd line of ART available, and (iii) decreasing the rate of withdrawal from care. Lastly, the following parameter changes made little difference in projected cumulative 15-year mortality in either strategy: (i) using HIV RNA monitoring, (ii) increasing the CD4 threshold for switching to 2nd-line ART, and (iii) continuing the CD4 gain on ART beyond 5 years or until current CD4 count reached 1500 cells/ μ L. None of these variations led to higher 15-year mortality on immediate ART compared to WHO 2010 ART.

Figure 2 shows one-way sensitivity analyses where **15-year mortality became higher with immediate ART as compared to WHO 2010 ART**. There were three key input parameters that made 15-year mortality in the immediate ART strategy worse than that in the WHO 2010 ART strategy: the annual rate of fatal toxicity from ART (Figure 2A), the rate of virologic failure, assuming that the rate of virologic failure was higher in patients on immediate ART than in those on WHO 2010 ART (Figure 2B), and the rate of withdrawal from care, assuming that the rate of withdrawal was higher in patients on immediate ART than in those on WHO 2010 ART (Figure 2C). The minimal annual rate of fatal toxicity from ART required to make mortality higher on immediate ART than on WHO 2010 ART was 1.0 per 100 person-years (Figure 2A). Assuming similar rates of withdrawal from care **or** virologic failure in both strategies, we were unable to find any rate at which 15-year mortality on immediate ART exceeded 15-year mortality on WHO 2010 ART (results not shown). However, when we assumed that the rates of virologic failure **or** withdrawal from care were higher in patients on immediate ART than in those on WHO 2010 ART, we found that with rates of ART failure > 4.3-fold higher (Figure 2B) or rates of withdrawal from care > 1.2-fold higher (Figure 2C) on immediate ART than on WHO 2010 ART, then 15-year mortality was higher on immediate ART than on WHO 2010 ART.

Three-way sensitivity analysis

We then varied these three key parameters together (Figure 3). Each bar in the figure represents a combination of values for these three parameters at which 15-year cumulative mortality with immediate ART is higher than 15-year mortality with WHO 2010 ART. For example, immediate ART led to higher 15-year mortality than WHO 2010 ART when

moderate rates of fatal ART toxicity (0.25/100PY) and a 1.1-fold increase in the rates of withdrawal from care on immediate ART compared to WHO 2010 ART were combined with rates of virologic failure on immediate ART >2.1-fold higher than that on WHO 2010 ART.

Discussion

We aimed to answer the following question: Could immediate ART produce more harm than benefit in HIV-infected adults living in sub-Saharan Africa?

We aimed to answer the following question: Could immediate ART produce more harm than benefit in HIV-infected adults living in sub-Saharan Africa? We restricted the question to patients who enter care with CD4 cell counts greater than 500 cells/ μ L, because this is the population for which the benefits/risks ratio of ART has not yet been proven. In Côte d'Ivoire, the probability for an adult recently infected with HIV-1 to have more than 500 CD4 cells/ μ L is 43% 9 months after seroconversion, 25% 4 years after seroconversion and 14% 8 years after seroconversion [Minga, AIDS 2011]. Though a minority, the group of patients who currently enter care with a CD4 count greater than 500 cells/ μ L is not a small group, even under current conditions of access to HIV testing. For instance, in Côte d'Ivoire, more than 25% of HIV-infected pregnant women who test HIV-positive during prenatal voluntary counseling and testing have a CD4 count greater than 500 cells/ μ L [Ekouevi et al, JAIDS 2004]. Patients in care with CD4 greater than 500 cells/ μ L are likely to become a sizable group if earlier identification of HIV-infected individuals and immediate ART initiation, regardless of CD4 count ("test and treat") proves to be effective in reducing HIV transmission.^{2,4} This strategy would be unethical, however, if the individual risks associated with very early ART initiation outweighed the individual and population benefits. Several randomized trials are ongoing to compare the individual outcomes of early ART initiation with those resulting from the current standard of care for ART initiation.^{4, 11, 12} The results of these trials will not be available until the end of 2013. In anticipation of these results, we used a simulation model to compare outcomes from very early ART initiation to currently recommended ART initiation thresholds.

Although model-based evaluations cannot replace randomized controlled trials, they complement clinical studies in two ways. First, models allow for the projection of long-term outcomes beyond the timeframe of randomized clinical trials. Long-term projection is particularly critical in evaluating lifelong interventions, since short-term outcomes may differ from long-term ones. Second, models allow for the variation of each key parameter likely to influence the outcomes of an intervention, which enables "what if" analyses on the impact of particular parameters. Thus, models allow for the examination of many more scenarios than randomized trials could actually test. Further, this "what if" approach can be useful to test the robustness of the main results of a completed clinical trial to different circumstances.²¹ This approach can also be useful to evaluate clinical trials before they are completed, to anticipate next steps and to identify the questions likely to arise as a consequence of the trial results.

In this study, we used the CEPAC-International model for both purposes – long term projection and "what if" analysis. While the ongoing immediate versus deferred ART trials will last up to five years at most, our main outcome was mortality at 15 years. The main objective was to determine if there are any credible scenarios in which immediate ART initiation could lead to higher mortality than the standard of care, assuming that the ongoing trials can only measure a limited number of the many scenarios in the field over the limited trial horizon. We chose 15-years as the time horizon, because poor adherence or withdrawal from care may have long-term consequences, and the individual benefits/risks ratio of

starting ART very early as compared to starting ART according to current WHO criteria may vary over time. The likelihood of finding parameters that would lead to more death with immediate ART than with WHO 2010 ART was higher at 15-year than at 5-year, as shown by the fact that the relative difference of %dead between the immediate ART strategy and the WHO2010 strategy decreased over time.

Two main messages can be drawn from the simulation.

First, ongoing trials will likely find that initiating ART very early, regardless of CD4 count, improves survival in sub-Saharan African adults; this outcome is likely to remain true long after the trials are finished. This result is robust to wide variations in input parameters, including treatment strategies (number and efficacy of available regimens, laboratory and clinical monitoring, and ART regimen switching criteria); incidence of HIV-related diseases; initial CD4 distribution; adherence to ART, withdrawal from care, and ART-related toxicity.¹³ For example, we estimated that the rate of fatal ART-related toxicity would have to be 1.0/100 person-years – very unlikely to be clinically viable – to make 15-year mortality higher in patients initiating ART immediately than in patients initiating ART according to the current standard of care.

Second, immediate ART is likely to remain more attractive than the standard of care as long as retention in care and virologic suppression rates are similar in both strategies. However, in some plausible scenarios, a combination of increased withdrawal from care and decreased virologic suppression due, for instance, to poorer treatment adherence among patients starting early, would outweigh the benefits of early ART and make it less effective than the current standard of care.

The individual benefits and risks of early ART depend to a large extent on context. On the one hand, the frequency of HIV-related diseases has a strong impact on the potential benefits of immediate ART. The benefits of starting ART early are expected to be higher in sub-Saharan Africa than in Western Europe or North America, given that tuberculosis and invasive bacterial diseases are the leading causes of death in HIV-infected, sub-Saharan African adults.^{9,10}

At the same time, the availability and quality of care, including drug toxicity management, ART regimen availability, and the risk of non-adherence and withdrawal from care have a major impact on the risks associated with immediate ART. In high-income countries, when patients experience adverse effects or virologic failure on one ART regimen, they have access to many well-tolerated drugs. In contrast, patients in low-income settings have access only to a limited number of drugs and tools for monitoring drug-related intolerance and virologic failure. The challenges associated with receiving prescribed drugs, including financial strain and the burden on work and family life are also greater for these patients, who are often forced to withdraw from ART programs after starting therapy.³⁷ In this context, starting ART too early may reduce the availability of efficient ART regimens later on in disease progression, when patients need them most.

This analysis has several limitations. First, we assumed that key parameters – including available treatment regimens, fatal toxicity, withdrawal from care, and virologic failure – were constant over time and homogeneous in the population. However, we believe that our choice of a long term cumulative outcome, together with the wide variation we applied to these parameters in sensitivity analysis, allows us to draw credible conclusions regarding how they will influence the difference in 15-year mortality between immediate ART and WHO 2010 ART. Second, even though one-way sensitivity analysis allowed wide variation in parameter values, we did not consider all possible combinations of parameter variation in multi-way sensitivity analysis. Instead, we focused our multi-way sensitivity analysis on the

treatment parameters that we found to be most critical to driving the difference in 15-year mortality between immediate ART and WHO 2010 ART. Third, we used input data from different sources in Côte d'Ivoire. Sensitivity analyses demonstrate that the major conclusions are robust to variation in these data estimates within plausible ranges. Fourth, it should be borne in mind that models are also based on parameters from limited data, and long-time estimates necessarily require assumptions derived from short-term data but applied in the long-term.

Modeling the impact of hypothetical interventions using data from observational studies can be done by other methods than CEPAC, including reanalysis of an existing study using the parametric g-formula (8). However, in sub-Saharan Africa, it is not possible to get all inputs that are needed for such analysis from standardized databases of large cohort collaborations, contrary to what has been successfully done in industrialized countries. In countries such as Côte d'Ivoire, though, it is possible to gather good quality inputs data from separate clinical trials and cohort studies. Because models such as CEPAC make it possible to use input data from multiple sources, we believe they are well adapted to the context of developing countries.

In conclusion, our findings have two practical consequences: First, “test and treat” trials aimed at evaluating the effect of immediate ART initiation on HIV transmission at the population level are appropriate to begin before the results of trials assessing the individual benefits of immediate ART become available, because immediate ART is highly likely to have more clinical benefits than risks at the individual level.

Second, in both “test and treat” and “when to start” trials, adherence and retention will be critical secondary outcomes. Differences between arms in terms of adherence and/or retention should be a focus of the trials, even in the absence of mortality differences over the time span of the trial. Differences in adherence and retention in the short-term may lead to differences in mortality in the long-term. If immediate ART proves to be beneficial, high levels of patient adherence and retention in care will be critical to ensure that patient-level benefits associated with immediate ART continue to outweigh the risks over time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents; Recommendations for a public health approach (2010 version). 2010. Available from: <http://www.who.int/hiv/pub/arv/adult2010/en/index.html>
2. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet*. 2009; 373:48–57. [PubMed: 19038438]
3. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *N Engl J Med*. 2011; 365:493–505. [PubMed: 21767103]
4. Walensky RP, Paltiel AD, Losina E, Morris BL, Scott CA, Rhode ER, et al. Test and treat DC: forecasting the impact of a comprehensive HIV strategy in Washington DC. *Clin Infect Dis*. 2010; 51:392–400. [PubMed: 20617921]
5. El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006; 355:2283–96. [PubMed: 17135583]
6. Kitahata MM, Gange SJ, Abraham AG, Merriman B, Saag MS, Justice AC, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med*. 2009; 360:1815–26. [PubMed: 19339714]
7. Sterne JA, May M, Costagliola D, de Wolf F, Phillips AN, Harris R, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet*. 2009; 373:1352–63. [PubMed: 19361855]
8. Cain L, Logan R, Robins J, Sterne J, Sabin C, Bansi L, et al. When to initiate combined antiretroviral therapy to reduce mortality and AIDS-defining illness in HIV-infected persons in developed countries: an observational study. *Ann Intern Med*. 2011; 154:509–15. [PubMed: 21502648]
9. Danel C, Moh R, Minga A, Anzian A, Ba-Gomis O, Kanga C, et al. CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in west Africa (Trivacan ANRS 1269 trial): a randomised trial. *Lancet*. 2006; 367:1981–9. [PubMed: 16782488]
10. Anglaret X, Minga A, Gabillard D, Ouassa T, Messou E, Morris B, et al. AIDS and Non-AIDS Morbidity and Mortality Across the Spectrum of CD4 Cell Counts in HIV-Infected Adults Before Starting Antiretroviral Therapy in Cote d'Ivoire. *Clin Infect Dis*. 2012; 54:714–723. [PubMed: 22173233]
11. Hargrove JW, Humphrey JH. Mortality among HIV-positive postpartum women with high CD4 cell counts in Zimbabwe. *AIDS*. 2010; 24:F11–4. [PubMed: 20095074]
12. Williams BG, Hargrove JW, Humphrey JH. The benefits of early treatment for HIV. *AIDS*. 2010; 24:1790–1. [PubMed: 20588108]
13. Braithwaite RS, Roberts MS, Goetz MB, Gibert CL, Rodriguez-Barradas MC, Nucifora K, et al. Do benefits of earlier antiretroviral treatment initiation outweigh harms for individuals at risk for poor adherence? *Clin Infect Dis*. 2009; 48:822–6. [PubMed: 19210173]
14. ANRS - French National Agency for Research on AIDS and Viral Hepatitis. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000. Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-infected Adults (ANRS 12136 TEMPRANO). Available from: <http://www.clinicaltrials.gov/ct2/show/NCT00495651> [cited 2010 Nov 08]
15. University of Minnesota CaTSI Strategic Timing of Antiretroviral Treatment (START). ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT00867048> [cited 2010 Nov 08]
16. Walensky RP, Wood R, Ciaranello AL, Paltiel AD, Lorenzana SB, Anglaret X, et al. Scaling up the 2010 World Health Organization HIV Treatment Guidelines in resource-limited settings: a model-based analysis. *PLoS Med*. 2010; 7:e1000382. [PubMed: 21209794]

17. Goldie SJ, Yazdanpanah Y, Losina E, Weinstein MC, Anglaret X, Walensky RP, et al. Cost-effectiveness of HIV treatment in resource-poor settings--the case of Cote d'Ivoire. *N Engl J Med*. 2006; 355:1141–53. [PubMed: 16971720]
18. Yazdanpanah Y, Losina E, Anglaret X, Goldie SJ, Walensky RP, Weinstein MC, et al. Clinical impact and cost-effectiveness of co-trimoxazole prophylaxis in patients with HIV/AIDS in Côte d'Ivoire: a trial-based analysis. *AIDS*. 2005; 19:1299–1308. [PubMed: 16052085]
19. World Health Organization. Antiretroviral Therapy For HIV Infection in adults and adolescents: Recommendations for a public health approach. 2006 revision. 2006. Available from: <http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf>
20. Kimmel AD, Weinstein MC, Anglaret X, Goldie SJ, Losina E, Yazdanpanah Y, et al. Laboratory monitoring to guide switching antiretroviral therapy in resource-limited settings: clinical benefits and cost-effectiveness. *J Acquir Immune Defic Syndr*. 2010; 54:258–68. [PubMed: 20404739]
21. Yazdanpanah Y, Wolf LL, Anglaret X, Gabillard D, Walensky RP, Moh R, et al. CD4+ T-cell-guided structured treatment interruptions of antiretroviral therapy in HIV disease: projecting beyond clinical trials. *Antivir Ther*. 2010; 15:351–61. [PubMed: 20516555]
22. Minga A, Danel C, Abo Y, Dohoun L, Bonard D, Coulibaly A, et al. Progression to WHO criteria for antiretroviral therapy in a 7-year cohort of adult HIV-1 seroconverters in Abidjan, Cote d'Ivoire. *Bull World Health Organ*. 2007; 85:116–23. [PubMed: 17308732]
23. Minga AK, Lewden C, Gabillard D, Bomisso GI, Toni TD, Emieme AA, et al. CD4 cell eligibility thresholds: an analysis of the time to antiretroviral treatment in HIV-1 seroconverters. *AIDS*. 2011; 25:819–23. [PubMed: 21412060]
24. Anglaret X, Chêne G, Attia A, Toure S, Lafont S, Combe P, et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Côte d'Ivoire: a randomised trial. *Lancet*. 1999; 353:1463–8. [PubMed: 10232311]
25. World Health Organization. World Mortality in 2000: Life Tables for 191 Countries. Geneva: World Health Organization; 2002.
26. Toure S, Kouadio B, Seyler C, Traore M, Dakoury-Dogbo N, Duvignac J, et al. Rapid scaling-up of antiretroviral therapy in 10,000 adults in Cote d'Ivoire: 2-year outcomes and determinants. *AIDS*. 2008; 22:873–82. [PubMed: 18427206]
27. Messou E, Chaix ML, Gabillard D, Minga A, Losina E, Yapo V, et al. Association between medication possession ratio, virologic failure and drug resistance in HIV-1-infected adults on antiretroviral therapy in Cote d'Ivoire. *J Acquir Immune Defic Syndr*. 2011; 56:356–64. [PubMed: 21191309]
28. Hunt PW, Deeks SG, Rodriguez B, Valdez H, Shade SB, Abrams DI, et al. Continued CD4 cell count increases in HIV-infected adults experiencing 4 years of viral suppression on antiretroviral therapy. *AIDS*. 2003; 17:1907–15. [PubMed: 12960823]
29. Moore RD, Keruly JC. CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. *Clin Infect Dis*. 2007; 44:441–6. [PubMed: 17205456]
30. WHO. WHO Expert Consultation on Cotrimoxazole Prophylaxis in HIV Infection. WHO technical report series. Reference number: WHO/HIV/2006.01. <http://www.who.int/hiv/pub/meetingreports/ctxprophylaxismeeting.pdf>
31. Mellors JW, Munoz A, Giorgi JV, Margolick JB, Tassoni CJ, Gupta P, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med*. 1997; 126:946–54. [PubMed: 9182471]
32. Losina E, Yazdanpanah Y, Deuffic-Burban S, Wang B, Wolf LL, Messou E, et al. The independent effect of highly active antiretroviral therapy on severe opportunistic disease incidence and mortality in HIV-infected adults in Cote d'Ivoire. *Antivir Ther*. 2007; 12:543–51. [PubMed: 17668563]
33. Seyler C, Messou E, Gabillard D, Inwoley A, Alioum A, Anglaret X. Morbidity before and after HAART initiation in Sub-Saharan African HIV-infected adults: a recurrent event analysis. *AIDS Res Hum Retroviruses*. 2007; 23:1338–47. [PubMed: 18184075]

34. Cole SR, Hernan MA, Margolick JB, Cohen MH, Robins JM. Marginal structural models for estimating the effect of highly active antiretroviral therapy initiation on CD4 cell count. *Am J Epidemiol.* 2005; 162:471–8. [PubMed: 16076835]
35. Danel C, Moh R, Chaix ML, Gabillard D, Gnokoro J, Diby CJ, et al. Two-months-off, four-months-on antiretroviral regimen increases the risk of resistance, compared with continuous therapy: a randomized trial involving West African adults. *J Infect Dis.* 2009; 199:66–76. [PubMed: 18986246]
36. Ekouevi DK, Rouet F, Becquet R, Inwoley A, Viho I, Tonwe-Gold B, et al. Immune status and uptake of antiretroviral interventions to prevent mother-to-child transmission of HIV-1 in Africa. *J Acquir Immune Defic Syndr.* 2004; 36:755–7. [PubMed: 15167296]
37. Boyer S, Marcellin F, Ongolo-Zogo P, Abega SC, Nantchouang R, Spire B, et al. Financial barriers to HIV treatment in Yaounde, Cameroon: first results of a national cross-sectional survey. *Bull World Health Organ.* 2009; 87:279–87. [PubMed: 19551236]
38. Mocroft A, Phillips A, Gatell J, Ledergerber B, Fisher M, Clumeck N, et al. Normalisation of CD4 counts in patients with HIV-1 infection and maximum virological suppression who are taking combination antiretroviral therapy: an observational cohort study. *Lancet.* 2007; 370:407–13. [PubMed: 17659333]
39. Tarwater PM, Margolick JB, Jin J, Phair JP, Detels R, Rinaldo C, et al. Increase and plateau of CD4 T-cell counts in the 3(1/2) years after initiation of potent antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2001; 27:168–75. [PubMed: 11404539]
40. Kaufmann GR, Furrer H, Ledergerber B, Perrin L, Opravil M, Vernazza P, et al. Characteristics, determinants, and clinical relevance of CD4 T cell recovery to <500 cells/microL in HIV type 1-infected individuals receiving potent antiretroviral therapy. *Clin Infect Dis.* 2005; 41:361–72. [PubMed: 16007534]
41. Valdez H, Connick E, Smith KY, Lederman MM, Bosch RJ, Kim RS, et al. Limited immune restoration after 3 years' suppression of HIV-1 replication in patients with moderately advanced disease. *AIDS.* 2002; 16:1859–66. [PubMed: 12351945]
42. Seyler C, Adje-Toure C, Messou E, Dakoury-Dogbo N, Rouet F, Gabillard D, et al. Impact of genotypic drug resistance mutations on clinical and immunological outcomes in HIV-infected adults on HAART in West Africa. *AIDS.* 2007; 21:1157–64. [PubMed: 17502726]

Figure 1. Main outcomes in the base case analysis

Cumulative mortality and mean CD4 count over a 15-year time horizon in patients with CD4 counts >500 cells/μL at first contact, according to different strategies of ART initiation.

Figure 1A. Cumulative risk of mortality over time.

Figure 1B. Mean CD4 count in patients alive at the end of each year

Figure 2. One-way sensitivity analysis on key parameters

Relative percent difference in mortality at 15 years between immediate ART and WHO 2010 guidelines ART, according to different values of key parameters:

Figure 2A. Rates of fatal ART toxicity.

Figure 2B. Ratios of ART failure rates (immediate ART/WHO 2010 ART).

Figure 2C. Ratios of withdrawal from care rates (immediate ART/WHO 2010 ART).

These figures show the impact of fatal ART toxicity, adherence-related ART failure, and withdrawal from care on the difference in 15-year mortality in the immediate ART strategy relative to the WHO 2010 strategy. Fatal ART toxicity varies the same way in the immediate ART strategy and in the WHO 2010 strategy; ART failure and withdrawal from care vary only for the immediate ART strategy and as multiples of the WHO 2010 strategy base-case values (See Results section for details).

PY: person-years

Relative percent difference: $1 - [\% \text{ dead at 15 years with immediate ART} / \% \text{ dead at 15 years with WHO 2010 ART}]$

Figure 3. Multi-way sensitivity analysis on key input parameters

This figure displays the combinations of fatal ART toxicity, withdrawal from care, and adherence-related ART failure that yield higher 15-year mortality in the immediate ART strategy than in the standard of care. Withdrawal from care and adherence-related ART failure vary only for the immediate ART strategy and as multiples of the WHO 2010 strategy base-case values.

PY: person-years

Table 1
Key inputs for an analysis of benefits and risks of immediate ART in Côte d'Ivoire

	Base case value	Ref	Sensitivity analysis range
Baseline cohort characteristics			
Age, mean (SD) years	31.7 (7.7)	22	31.7 (7.7) to 25.0 (7.7)
Sex distribution (% men)	38	9,35	-
VL distribution	See footnote ⁽¹⁾	22	-
CD4 cells/ μ L (SD)	609 (82)	UNP ⁽²⁾	609 (82) to 700 (5)
HIV morbidity and mortality count, mean, by CD4 count	See appendix 2	9,35	1.0 $\times$ to 1.5 $\times$ base case
Effect of ART on morbidity/mortality ⁽³⁾	On ART = 0.393 $\times$ off ART	32,33	On ART = 0.393 to 1.0 $\times$ off ART
Number of lines of ART available	2	26	1 line to 3 lines
Monitoring of patients on ART	CD4 every 6 months	26	CD4 and VL every 6 months
ART switching criteria	World Health Organization criteria	19	Alternative combinations of VL, CD4 & clinical criteria
ART efficacy			
<i>Immunologic, 1st and 2nd line</i>			
CD4 gain at 6 months, mean (SD) cells/ μ L	+136 (136)	26	0.5 $\times$ base case
Monthly CD4 increase, mean (SD) cells/ μ L			
6 months to 5 years	+3.04 (0.76)	26	0.5 $\times$ base case
> 5 years	0	29	0 (0) to 3.04 (0.76) (4)
CD4 ceiling, maximum cells/ μ L	1200	ASMP	1200 to 1500
<i>Virologic, 1st line⁽⁵⁾</i>			
HIV RNA suppression at 6 months, %	80.4	26	0.5 $\times$ base case
Failure after 6 months./100 PY	15.6	26	1.0 to 10.0 $\times$ base case
<i>Virologic, 2nd line</i>	= 1st line	ASMP	0.5 $\times$ 1st line
ART fatal toxicity./100 PY⁽⁶⁾	0	ASMP	0.1 to 2.0
Withdrawal from care of patients on ART⁽⁵⁾			
0-12 months./100 PY	11.6	26	0.0 to 3.0 $\times$ base case
>12 months./100 PY	9.2	26	0.0 to 3.0 $\times$ base case
Probability of return to care with severe OI once withdrawn	50%	ASMP	0% - 50%

ART: antiretroviral therapy

PY: person-years

ASMP: assumption

UNP: unpublished

VL: plasma HIV-1 RNA viral load

⁽¹⁾ Viral load distribution at baseline was as follows: 24% of the population had VL of more than 100,000 copies/mL; 31% had VL between 30,001 and 100,000 copies/mL; 16% had VL between 10,001 and 30,000 copies/mL; 15% had VL between 3,001 and 10,000 copies/mL; 8% had VL between 501 and 3,000 copies/mL; 5% of the population had VL below 501 copies/mL.

- (2) CD4 count distribution in HIV-infected adults with a CD4 count >500 cells/ μ L at first contact in Côte d'Ivoire: IeDEA West Africa database [Eric Ballestre, personal communication].
- (3) ART effect: reduction in all CD4-specific rates of severe morbidity reported in patients on ART, as compared to those not on ART.^{32,33}
- (4) In the base case analysis, we assumed that there was a plateau effect, with no CD4 count increase in patients on ART after 5 years of treatment;³⁸⁻⁴¹ in sensitivity analysis, we assumed no plateau effect and a continued increase of + 3.04 CD4 cells/ μ L per month.
- (5) In the base case analysis, we assumed that adherence to ART was equivalent in the immediate ART and WHO 2010 ART strategies, leading to equivalent rates of virologic failure. In sensitivity analysis, we assessed what would happen if patients starting ART very early were less adherent, leading to higher rates of virologic failure in immediate ART strategy compared to WHO 2010 ART. Similarly, in the base case analysis, we assumed that retention in care was equivalent in immediate ART and in WHO 2010 ART, leading to equivalent rates of withdrawal from care. In sensitivity analysis, we explored what would happen if patients starting ART very early had lower retention in care, leading to higher rates of withdrawal from care in immediate ART strategy compared to WHO 2010 ART.
- (6) ART-related fatal toxicity: we assumed that a given rate of death occurring on ART could be directly related to acute or chronic toxicity (renal, liver, allergic or cardiovascular) of antiretroviral drugs. In the base case, we assumed no such fatal toxicity; in sensitivity analysis, we used a "what if" approach and varied the fatal toxicity rate widely, determining the threshold of fatal toxicity at which mortality at 15 years would be higher with immediate ART than with WHO 2010 ART.

Table 2
15-year mortality in patients initiating ART immediately and in those initiating ART by WHO 2010 guidelines: base case outcomes and select one-way sensitivity analyses

	% dead at 15 years		
	ART initiation		Relative percent difference*
	WHO 2010	Immediate	
Base case results	56.7	51.8	-8.6
One-way sensitivity analyses			
Baseline cohort characteristics			
Mean age 25.0 years (SD 7.7)	55.3	50.2	-9.2
Mean CD4 count 700 cells/ μ L (SD 5)	51.4	46.1	-10.3
HIV morbidity and mortality			
Mortality from opportunistic diseases = 1.5 $\times$ base case	58.4	53.5	-8.4
No direct effect of ART on morbidity/mortality	66.2	59.4	-10.3
Number of lines of ART available			
One line	69.9	67.2	-3.9
Three lines	56.6	51.6	-8.8
HIV RNA-based ART switching criteria			
1 log increase from nadir	56.3	52.0	-7.5
CD4 count-based ART switching criteria			
50% decline from peak or CD4 <200 cells/ μ L	56.6	51.7	-8.6
ART efficacy			
Immunologic			
CD4 gain = 0.5 $\times$ base case	61.4	55.7	-9.3
Continued CD4 increase >5 years	56.4	51.6	-8.6
CD4 ceiling 1500 cells/ μ L	56.6	51.8	-8.6
Virologic**			
6-month VL suppression on 1 st and 2 nd line = 0.5 $\times$ base case	68.6	65.7	-4.4
Rate of failure after six month = 2.0 $\times$ base case	58.2	53.4	-8.2
6-month VL suppression on 2 nd line = 0.5 $\times$ 1 st line	60.0	56.0	-6.7
Withdrawal from care on ART*			
No withdrawal from care	33.4	23.8	-28.5
Withdrawal from care = 2.0 $\times$ base case	70.1	67.2	-4.2
No return to care once withdrawn from care	61.2	57.4	-6.2

* Relative percent difference: 1-[%dead at 15 years with immediate ART/%dead at 15 years with WHO 2010 ART]

ART: antiretroviral therapy

PY: person-years

VL: plasma HIV-1 RNA viral load

** We assumed similar rates of withdrawal from care and virologic failure in the immediate ART strategy and in the WHO 2010 ART strategy.