Published in final edited form as:

Antivir Ther. 2010 ; 15(3): 351–361. doi:10.3851/IMP1542.

CD4-guided structured treatment interruptions of antiretroviral therapy in HIV disease: Projecting beyond clinical trials

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Author contributions: YY, LLW, XA, RPW, EL and KAF contributed to the conception and design of the study. XA, DG, RM and CD acquired data for the study. DG and EL performed analysis of trial data. YY, LLW, XA, RPW, EL and KAF designed the model-based analysis. LLW and CES performed the model-based analysis. All authors participated in interpretation of results. YY, LLW and CES drafted the article. All authors revised the article critically for important intellectual content. All authors have given final approval for publication.

Abstract presented at the XVII International AIDS Conference in Mexico City August 3-8, August 2008 [Abstract TUPE0130].

Potential Conflicts of Interest: With the exception of Dr. Yazdanpanah, none of the authors report any association that might pose a conflict of interest (e.g. pharmaceutical stock ownership, consultancy, advisory board membership, relevant patents, or research funding). Dr. Yazdanpanah has received travel grants, honoraria for presentation at workshops and consultancy honoraria from Bristol-Myers Squibb, Gilead, Glaxo-SmithKline, Merck, Pfizer, Roche and Tibotec.

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For the CEPAC-International Investigators

Abstract

Background—International trials have shown that CD4-guided structured treatment interruptions (STI) of antiretroviral therapy (ART) lead to worse outcomes than continuous treatment. We simulated continuous ART and STI strategies with higher CD4 interruption/reintroduction thresholds than those assessed in the trials.

Methods—We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) Model to simulate cohorts of African adults with different CD4 counts at presentation ($\leq 200/\mu\text{l}$, 201–350/ μl , 351–500/ μl). We varied ART initiation criteria (immediate, $\text{CD4} < 350/\mu\text{l}$ or severe opportunistic event, $\text{CD4} < 200/\mu\text{l}$ or severe opportunistic event), and ART interruption/reintroduction CD4 thresholds (e.g. 350/250/ μl , 500/350/ μl , 700/500/ μl). First-line therapy was non-nucleoside reverse transcriptase inhibitor (NNRTI)-based and 2nd-line was protease inhibitor (PI)-based.

Results—STI generally led to a lower life expectancy than continuous ART, regardless of ART initiation criteria and interruption/reintroduction thresholds. Life expectancy increased with earlier ART initiation and higher interruption/reintroduction thresholds. STI reduced life expectancy by 48–69 months and by 11–30 months, compared to continuous ART when interruption/reintroduction thresholds were 350/250/ μl and 500/350/ μl , depending on ART initiation criteria. When patients interrupted/reintroduced ART at $\text{CD4} 700/500/\mu\text{l}$, life expectancies for STI ranged from 2 months lower to 1 month higher than continuous ART. Life expectancy for patients on STI increased with decreased risk of virologic resistance after ART interruptions.

Conclusions—STI with NNRTI-based regimens was almost always less effective than continuous treatment, regardless of interruption/reintroduction thresholds. The risks associated with STI decrease only if patients start ART earlier, interrupt/reintroduce treatment at very high CD4 thresholds (700/500/ μl) and use first-line medications with higher resistance barriers, such as PIs.

Keywords

Africa; antiretroviral therapy; CD4-guided structured treatment interruptions; models/projections

Introduction

In high-income countries, antiretroviral therapy (ART) has led to a dramatic decrease in morbidity and mortality in patients infected with the human immunodeficiency syndrome (HIV) [1, 2]. However, ART is often associated with short-term and long-term adverse

events that can lead to poor adherence and drug resistance. These obstacles motivated several randomized trials to assess the use of structured treatment interruptions (STI) to prevent ART toxicity while maintaining the same efficacy as continuous treatment [3, 4]. Two randomized STI trials conducted in sub-Saharan Africa [4, 5] assessed outcomes in settings with higher rates of early HIV-related morbidity than in resource-rich countries [3, 6, 7].

STI strategies can be guided either by individual CD4 count or by time on therapy. Recent studies investigating CD4-guided STI, both outside of Africa (SMART) [3] and in Africa (Trivacan) [4], were designed to interrupt ART at CD4 counts $>350/\mu\text{l}$ and restart ART when CD4 counts dropped to $<250/\mu\text{l}$. Both trials were stopped early because of evidence that patients on STI were at a significantly higher risk of severe clinical events and death compared to continuous ART [3, 4]. However, it is unclear from these studies whether STI would have shown better results if they had examined different CD4-guided strategies [3, 8–10]. Moving forward, new clinical trials aimed at assessing alternative interruption/reintroduction thresholds would be time-consuming and expensive and could be considered unethical, given the results of the SMART and Trivacan trials [3, 4]. Our objective was to use a simulation model to assess different plausible STI strategies compared to continuous ART in Côte d'Ivoire, West Africa.

Methods

Analytic overview

Using a computer-based simulation model of HIV disease and treatment, we investigated the impact of different CD4-guided STI strategies on outcomes in HIV-infected patients in Côte d'Ivoire [11–15]. We evaluated HIV treatment strategies for three hypothetical cohorts of patients who presented to care with CD4 counts $\leq 200/\mu\text{l}$, $201–350/\mu\text{l}$ and $351–500/\mu\text{l}$. For each of these cohorts, we assessed three aspects of care: 1) ART initiation criteria (immediate, CD4 $<350/\mu\text{l}$ or severe opportunistic event, and CD4 $<200/\mu\text{l}$ or severe opportunistic event); 2) CD4 count thresholds for interrupting ART ($350/\mu\text{l}$, $500/\mu\text{l}$, and $700/\mu\text{l}$); and 3) CD4 count thresholds for reintroducing ART after CD4 declined during interruptions ($250/\mu\text{l}$, $350/\mu\text{l}$, and $500/\mu\text{l}$; Table 1). We also projected outcomes for patients who remained on continuous treatment after initiating ART. We compared outcomes of STI and continuous ART in patients with similar CD4 counts at presentation and ART initiation. The primary outcome of the analysis was life expectancy, in life-months. We also assessed costs in 2007 US dollars, **from model entry until death**. We adopted a modified societal perspective, excluding patient time and travel in our estimation of costs. We report undiscounted life expectancies, as well as life expectancies and costs discounted at 3% per year [16].

Model overview

The Cost-Effectiveness of Preventing AIDS Complications (CEPAC) International Model is a first-order state-transition Monte Carlo simulation of the natural history, clinical management, outcomes, and costs of HIV disease [11, 12, 15]. The model simulates HIV disease in several resource-limited settings, including Côte d'Ivoire. Monthly transitions between “health states” describe the natural history of disease. True CD4 count, HIV RNA level and history of **HIV-related conditions** determine disease progression. Death may be attributed to an acute opportunistic disease, HIV infection itself, or non-AIDS-related causes. Other model specifications have been published elsewhere in detail [12, 15].

For this analysis, we designed a new structural module to simulate STI. In this module, ART is interrupted and reintroduced according to pre-defined CD4 count criteria. CD4 change

during STI varies according to baseline HIV RNA, nadir CD4 count, and number of prior interruptions. Interruptions and reintroductions alternate until patients reach an STI endpoint or die. STI endpoints are defined as one severe opportunistic disease event or CD4 count decline to $<200/\mu\text{l}$, as in Trivacan [4].

Simulated Strategies

We considered two consecutive ART regimens, as per current standard-of-care in Côte d'Ivoire. First-line therapy was non-nucleoside reverse transcriptase inhibitor (NNRTI)-based and 2nd-line was protease inhibitor (PI)-based [4, 17]. Clinic visits and CD4 tests occurred every 2 months. We assumed that HIV RNA tests were not available for monitoring or decision making, since they are not routinely available in Côte d'Ivoire and in many other resource-limited settings. However, true CD4 count and HIV RNA level both determined disease progression, since the model tracked clinical, immunologic and virologic status monthly.

We evaluated strategies separately for patients presenting to care with CD4 counts $\leq 200/\mu\text{l}$, 201–350/ μl or 351–500/ μl . All patients who initiated care received cotrimoxazole. When patients became eligible for ART, they initiated treatment with continuous therapy (run in period, Figure 1). Patients who failed 1st-line therapy or who never reached the threshold for interruption were considered to be ineligible for STI [4]. These patients switched to 2nd-line therapy upon failing 1st-line therapy. When patients in the STI strategy were suppressed on 1st-line ART and reached the pre-defined CD4 threshold for interruption, they were taken off therapy. They remained off ART until they reached the CD4 threshold for reintroduction. They continued to cycle on and off 1st-line therapy until they reached any of three STI endpoints: 1) observed CD4 $<200/\mu\text{l}$ during an interruption, when the CD4 count threshold for reintroducing ART was 250/ μl ; 2) one severe **HIV-related** disease event; or 3) observed CD4 count decrease to $<200/\mu\text{l}$ while on ART, a proxy for virologic failure since HIV RNA tests were not available [4]. When the CD4 count threshold for reintroducing ART was 350/ μl or 500/ μl , patients could only reach endpoints 2 and 3, because the frequency of CD4 count tests prevented them from reaching $<200/\mu\text{l}$ during interruptions. After reaching an STI endpoint, patients resumed 1st-line NNRTI-based therapy without any new interruptions (Figure 1). Their virologic suppression rates differed depending on the STI endpoint they had reached. Patients switched to a 2nd-line PI-based regimen according to the main World Health Organization (WHO) clinical and immunological criteria for failure: 1) an observed 50% decline from peak on-treatment CD4 count, or 2) a new severe **HIV-related** disease (Figure 1) [18].

Cohort characteristics—The demographics of simulated patients matched the Trivacan trial [4]. Mean age was 35 years (SD = 8) and 21% of patients were men. At baseline, 47% of patients had HIV RNA $>100,000$ copies/ml. We simulated three different strata for initial CD4 counts, as described above.

Progression of HIV disease—When patients were off ART, CD4-stratified incidence rates of HIV-related conditions, including AIDS and severe non-AIDS diseases, were from the Cotrame (ANRS 1203) and Primo-CI (ANRS 1220) cohort studies and were the same for patients in the STI and continuous ART groups [6, 7]. We assumed that ART had an independent protective effect against severe HIV-related conditions diseases [19, 22]. In the absence of data from Côte d'Ivoire, we used data reported by the Multicenter AIDS Cohort Study in the United States to model monthly declines in CD4 count before ART initiation [23]. We estimated CD4 decreases during ART interruptions and increases after ART reintroductions from the CD4-guided STI arm of the Trivacan trial (Table 2) [4].

Efficacy of ART—The efficacy of continuous NNRTI-based 1st-line ART was derived from Trivacan, in which 87% of patients achieved HIV RNA <300 copies/ml at 6 months [17] and 0.18% failed virologically each month thereafter [20]. The mean CD4 count increase at 12 months was 152/ μ l (unpublished analysis) [20].

When patients in the STI strategy resumed continuous treatment, we considered NNRTI-based ART to be ineffective if they ended STI because their CD4 counts declined to <200/ μ l while on ART. We assumed that these patients had failed virologically and developed resistance to NNRTIs. If patients ended STI because their CD4 counts had declined to <200/ μ l during an interruption or because of a severe opportunistic event, NNRTI-based continuous ART was less effective, to account for the increased resistance attributable to STI [4, 20]. In these patients, the probability of failing to achieve HIV RNA levels <300 copies/ml on NNRTI-based ART after ending STI was defined as the risk of resistance attributable to each interruption (4 per 100 person-interruptions) multiplied by the number of interruptions, plus the monthly probability of virologic failure on ART (0.18%) [20]. For example a patient who ended STI after 3 interruptions and was on ART for 12 months during STI was estimated to have an 85.8% ($=100\%-[4\%*3]-[0.18\%*12]$) probability of becoming virologically suppressed upon resuming NNRTI-based ART.

We assumed that efficacy of 2nd-line ART was the same as 1st-line ART, since patients received one new drug class (PI) and two new NRTIs [17]. ART was considered to have a protective effect on severe morbidity and mortality independent of CD4 count [19, 22]. We assumed that ART led to no fatal toxicity events. We tested this assumption in sensitivity analysis.

Costs—We estimated costs of routine medical care in Côte d'Ivoire, including laboratory tests, clinic visits, hospital stays and treatment of acute opportunistic diseases and toxicities. These costs have been reported elsewhere [12, 15].

Sensitivity analyses—We performed extensive sensitivity analysis on major model parameters. Specifically, we evaluated the implications of alternative assumptions in areas lacking primary data, including CD4 changes for patients interrupting and reintroducing ART at CD4 counts higher than in Trivacan, the proportion of patients reaching each STI endpoint, and 2nd-line ART efficacy. We assessed the impact of variations in the **frequency of CD4 count tests**, the rate of fatal toxicity due to ART, and increased rates of morbidity during interruptions, as well as the impact of using PI-based ART during STI by reducing the risk of resistance to ART after returning to continuous treatment. We also varied region-specific parameters, such as the incidence of various opportunistic diseases, and the probability of acquiring non AIDS-related conditions during interruptions, to account for the increased risk of malignancies and cardiovascular diseases observed in the SMART trial [3, 8–10, 24]. Finally, we considered longer intervals between clinic visits, to account for potential variability in access to care.

Results

Model validation

We performed an internal validation analysis of our model by matching the mean CD4 counts over time of the simulated cohorts with data from the continuous ART and STI arms of the Trivacan trial. Model projections of CD4 counts were within 2% of reported trial results at 12 months and within 8% at 24 months (Technical Appendix, Figure A2).

Base case analysis

In a cohort of patients presenting to care with CD4 counts $\leq 200/\mu\text{l}$ (mean $100/\mu\text{l}$, SD $51/\mu\text{l}$) and starting ART immediately, STI was always less effective than continuous ART, regardless of interruption/reintroduction CD4 thresholds (Table 3). STI reduced undiscounted life expectancy by 11–48 months compared to continuous ART, depending on the interruption/reintroduction CD4 threshold.

In a cohort of patients presenting to care with CD4 counts $201\text{--}350/\mu\text{l}$ (mean $275/\mu\text{l}$, SD $51/\mu\text{l}$) or $>350/\mu\text{l}$ (mean $425/\mu\text{l}$, SD $51/\mu\text{l}$), CD4-guided STI was less effective or comparable to continuous treatment, depending on ART initiation criteria and interruption/reintroduction CD4 thresholds (Table 3). When we replicated the $350/250/\mu\text{l}$ interruption/reintroduction strategy of the Trivacan trial, STI resulted in mean undiscounted life expectancies 59–69 months lower than continuous ART, depending on CD4 count at presentation and ART initiation criteria. Patients who interrupted/reintroduced ART at CD4 $700/500/\mu\text{l}$ had mean life expectancies between 2 months lower and 1 month higher than patients on continuous ART. Patients who presented to care with CD4 counts $201\text{--}350/\mu\text{l}$ or $>350/\mu\text{l}$, started ART immediately and interrupted/reintroduced therapy at CD4 counts $700/500/\mu\text{l}$ interrupted ART an average of four times (standard deviation, 5), with interruptions lasting an average of 18 months. In both groups, patients spent 79% of their time on ART and 21% of their time off ART.

Figure 2 shows model-generated survival curves for patients starting ART immediately and presenting to care with CD4 counts $201\text{--}350/\mu\text{l}$ (Figure 2a) or $351\text{--}500/\mu\text{l}$ (Figure 2b). STI and continuous ART produced similar life expectancies in the first two years, but long-term projections **from entry into the model until death** suggest that continuous ART is better than STI in almost all cases. Long-term life expectancy estimates for STI were only comparable to continuous ART when patients interrupted ART at CD4 counts $>700/\mu\text{l}$ and reintroduced ART at CD4 counts $<500/\mu\text{l}$.

STI was always associated with lower costs than continuous ART (Table 3). When patients presented to care with CD4 counts $201\text{--}350/\mu\text{l}$, initiated ART immediately, interrupted ART at CD4 counts $>700/\mu\text{l}$ and reintroduced ART at CD4 counts $<500/\mu\text{l}$, per-person lifetime costs were \$2,200 lower than for continuous ART.

Sensitivity analyses

We performed sensitivity analyses on patients with initial CD4 counts of $201\text{--}350/\mu\text{l}$ and $>350/\mu\text{l}$ who started ART immediately and interrupted/reintroduced therapy at CD4 counts $700/500/\mu\text{l}$. Results were most sensitive to variations in the rate of ART-related fatal toxicity and the risk of resistance to ART after each interruption. If we assumed that the yearly rate of fatal ART toxicity was 0.6/100 person-years, based on reported rates of NNRTI-related fatal lactic acidosis in sub-Saharan Africa [27, 28], STI increased life expectancy by 5 months in patients with initial CD4 counts of $201\text{--}350/\mu\text{l}$ and 4 months in patients with initial CD4 counts $>350/\mu\text{l}$. When interrupting ART did not cause additional resistance compared to continuous ART, as may be the case if PI-based ART were used for the initial regimen, STI increased life expectancy by 11 and 15 months in each group. In these cases, STI became cost-saving compared to continuous treatment.

Results were less sensitive to variations in rates of severe non-AIDS diseases during STI, incidence of opportunistic diseases, morbidity events while on ART, and frequency of CD4 tests. Detailed results of these sensitivity analyses are in the technical appendix (Table A2, Figure A2). Our results were robust to wide variations in all parameters for which primary data were not available. These included: 1) CD4 changes for higher interruption/reintroduction thresholds than in Trivacan; 2) the proportion of patients reaching each STI

endpoint when interruption/reintroduction thresholds were higher; and 3) efficacy of 2nd-line ART (Technical Appendix).

Discussion

Interest in CD4-guided STI has increased, with studies suggesting that it could decrease ART-related toxicity and costs [29–33]. However, two recent randomized trials (SMART and Trivacan) found that STI was associated with higher **AIDS and severe non-AIDS** morbidity and mortality [3, 4, 9, 20, 34]. In these studies patients interrupted ART at CD4 counts >350/μl and restarted at CD4 counts <250/μl.

Although STI could be attractive at different thresholds for interruption and reintroduction, new STI trials are unlikely. Drawing on data from previous trials, we used a simulation model to evaluate the short- and long-term outcomes of alternative STI strategies in Côte d'Ivoire. We simulated patients with different CD4 counts at presentation to care, ART initiation, interruption and reintroduction. In almost all cases, STI was less effective than continuous ART, but differences in life expectancy between STI and continuous ART decreased with increasing thresholds. Patients on STI had life expectancies closest to continuous ART when they presented to care with CD4 counts >200/μl, initiated ART immediately and interrupted and reintroduced ART at very high CD4 counts (700/500/μl). The number and duration of interruptions was highly variable, however, suggesting that a strategy of fixed-time STI would not capture individual differences in CD4 count declines during ART interruptions and increases during ART reinitiations.

The results of this analysis are consistent with results from the SMART trial [3, 4]. However, our results contrast with outcomes from several STI trials outside Africa that interrupted and reintroduced ART at higher CD4 thresholds than SMART and Trivacan [29–33]. These studies found that when ART is interrupted at CD4 counts >350/μl (up to 700/μl in the recent randomised controlled LOnG Term Treatment Interruption [LOTTI] trial led by Maggiolo *et al.*) and reintroduced at CD4 counts ≤350/μl, reduced time spent at low CD4 counts may eliminate differences in survival between STI and continuous ART [35]. However, none of these studies had enough power to detect differences in morbidity and mortality rates, especially given their short duration. As illustrated in Figure 2, STI strategies with interruption/reintroduction thresholds at CD4 counts 500/350 and 700/350/μl may appear comparable to continuous ART in the short-run. **Longer-term projections over patients' lifetimes**, however, **suggest that** continuous ART is more effective than STI, even if ART is interrupted at CD4 counts >700/μl and reintroduced <350/μl. This finding is consistent with the results of a subgroup analysis in SMART showing that morbidity and mortality rates for STI and continuous ART were different, even at high CD4 counts [9]

Results were most sensitive to ART-related toxicity rates and risk of resistance to ART, especially when patients started ART at higher CD4 counts than currently recommended. When we assumed higher rates of fatal ART-related toxicity, STI produced results comparable to continuous ART in patients who interrupted/reintroduced ART at CD4 counts 700/500/μl. Although newer antiretroviral drugs associated with lower toxicity rates [36, 37] are rarely available in resource-limited countries, it is likely that low-cost but highly toxic drugs such as stavudine will soon be replaced with safer medications in these settings [27, 28, 38, 39]. Consequently, ART-related toxicity will decrease and the potential benefits of using STI to avoid toxicity will also decrease.

If we assumed a lower risk of resistance to ART during STI, then STI and continuous ART led to comparable outcomes when patients initiated ART at CD4 counts >350/μl and interrupted/reintroduced ART at CD4 counts 700/500/μl. This sensitivity analysis allowed

us to evaluate the impact of potentially implementing STI with PI-based ART. In Trivacan, 93% of patients in the CD4-guided STI arm started ART with an NNRTI-based regimen, most often in combination with zidovudine and lamivudine [4], NRTIs with differing half-lives. At interruption, NNRTIs were discontinued five days before NRTIs, but it is unclear whether this delay was enough to avoid resistance completely. Patients may have been on functional monotherapy for several days at the beginning of each interruption, which may have led to NNRTI resistance [20, 40–43]. Recently, studies have shown that it is possible to reduce the probability of virologic resistance after each interruption by replacing NNRTIs in 1st-line ART with a PI for a short time before interruption, because PIs have a shorter half-life and higher genetic barrier to resistance [44]. If the risk of virologic resistance to ART during STI declines to below the risk of resistance during continuous ART, one goal of STI could be to reduce resistance to ART by decreasing exposure to drugs. Reductions in resistance would be particularly valuable in low-income settings, where often only two ART regimens are available. However, because only three antiretroviral drug classes are available in these settings, the risk of resistance on a second-line regimen that contains recycled drugs will likely be much lower if it contains drugs with high genetic barriers, such as PIs, than drugs with low genetic barriers, such as NNRTIs. In addition, NNRTIs are often preferred for first-line ART because they are much more affordable than PIs [21].

This analysis has several limitations. First, data on mean CD4 count changes during interruption and reintroduction periods were from patients whose baseline characteristics corresponded to those in the Trivacan trial. We assumed that these changes would be similar at higher CD4 counts. Furthermore, the data from the trial were collected over a 24-month period and a mean of 2 interruptions/reintroductions [4, 20]. CD4 count declines during ART interruptions and increases during ART reintroductions in Trivacan may not be generalizable to patients with higher initial CD4 counts or additional cycles of ART interruptions and reintroductions. For example, in the SMART trial, which followed patients for a mean time of 16 months, CD4 counts declined 87 cells/ μ l/month in the first two months of interruption and increased 166 cells/ μ l/month in the first eight months of reinitiation [3]. The recent LOTTI trial showed that CD4 counts declined 13 cells/month/ μ l during a mean interruption time of 27 months [35]. In the BASTA trial, which interrupted ART at CD4 counts $>800/\mu$ l and reintroduced ART at CD4 counts $<400/\mu$ l, CD4 count declines varied by nadir CD4 count [30]. Second, patients in the STI strategy had an increased risk of non-AIDS diseases compared to patients on continuous ART, but only because their average CD4 counts were lower and because they did not benefit from the independent protective effect of ART during interruptions. The results remained stable when we increased the incidence of cardiovascular disease and malignancies in the STI group, but not in the continuous ART group, to twice that observed in SMART. Third, we did not consider STI scenarios in which HIV RNA testing might be available. If it were, patients on STI would perhaps have had a longer life expectancy since virologic failure would have been detected earlier, especially during treatment interruptions. Fourth, there are no published data on the efficacy of continuous NNRTI-based ART after it has been used for STI. We derived estimates for decreased ART efficacy using data on the rates of virologic resistance detected after each interruption in the fixed STI arm of Trivacan. We performed extensive sensitivity analyses on all of these parameters and found that they did not affect the main policy conclusions.

A randomized trial is ongoing in Côte d'Ivoire to evaluate the impact of ART initiation based on 2006 WHO guidelines vs. earlier initiation in HIV-infected patients [45]. If this trial shows that starting ART earlier is associated with better outcomes, ART initiation at higher CD4 counts might become the standard of care. Although this policy could reduce morbidity and increase life expectancy, long term ART-related toxicity, drug fatigue, non-adherence and societal costs will increase. This model-based analysis demonstrates that STI

could be comparable to continuous ART in Côte d'Ivoire if patients start ART with CD4 counts $>200/\mu\text{l}$, interrupt/reintroduce ART at CD4 counts 700/500/ μl , and use drugs with higher genetic barriers such as PIs. If ongoing trials in Côte d'Ivoire and other resource-limited settings move treatment guidelines to earlier in the course of disease, then physicians and patients may become more interested in using STI at very high CD4 interruption and reintroduction thresholds, when the risk of opportunistic disease events is low.

Acknowledgments

The authors gratefully acknowledge Sylvie Deuffic-Burban, Ph.D, Eugène Messou, MD, PhD, Bingxia Wang, PhD and Nomita Divi, MS for their assistance.

Financial support: This research was supported by grants from the Agence National de Recherches sur le SIDA (ANRS 1286 and 1269), the National Institute of Allergy and Infectious Diseases (R01 AI058736, K24 AI062476, P30 AI42851) and the Doris Duke Charitable Foundation Clinical Scientist Development Award. The funding sources had no role in the design, analysis, or interpretation of the study or in the decision to submit the manuscript for publication.

Supported by grants from the Agence National de Recherches sur le SIDA (ANRS 1286 and 1269), the National Institute of Allergy and Infectious Diseases (R01 AI058736, K24 AI062476, P30 AI42851) and the Doris Duke Charitable Foundation Clinical Scientist Development Award.

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Figure 1. Overview of an analysis of structured treatment interruptions (STI) compared to continuous antiretroviral therapy (ART) in Côte d'Ivoire. OD: opportunistic disease.

Figure 2.

Projected survival for patients with initial CD4 201–350/μl (2a) and CD4 351–500/μl (2b) initiating antiretroviral therapy (ART) immediately. Each line represents a different ART interruption/reintroduction threshold. The proportion of patients on continuous ART who were alive ten years after treatment initiation was 89.9% in the 201–350/μl CD4 cohort, while the proportions alive in the structured treatment interruptions (STI) arm after ten years were 90.0%, 85.8% and 74.9% when interruption/reintroduction CD4 thresholds were 700/500/μl, 500/350/μl and 350/250/μl. In patients presenting to care with CD4 351–500/μl, the proportion alive in the continuous arm was 91.3% after ten years; in the STI arm survival was 91.2% and 85.9% when interruption/reintroduction CD4 thresholds were 700/500/μl and 500/350/μl.

Table 1

Strategies evaluated in a simulation of structure treatment interruption trials

Initial CD4 count	ART initiation criteria	All interruption/reintroduction CD4 count combinations examined (μl) ^a
$\leq 200\mu\text{l}^b$	Immediate	350/250
		500/250
		500/350
201–350 μl	CD4 <200/ μl or severe OD	350/250
		500/250
		500/350
	Immediate	700/250
		700/350
		700/500
351–500 μl	CD4 <200/ μl or severe OD	350/250
		500/250
		500/350
		700/250
		700/350
351–500 μl	CD4 <350 μl or severe OD	700/500
		500/250
		500/350
		700/250
		700/350
	Immediate	700/500

OD: opportunistic disease

^a Only applicable to the structured treatment interruption arm.^b We did not evaluate strategies with interruption CD4 thresholds $\geq 700/\mu\text{l}$ in these patients, because the proportion of patients who reached this CD4 count was small (37%), as shown in previous studies [25, 26].

Table 2

Selected model input parameters for a simulation of CD4-guided STI in Côte d'Ivoire

Variable	Baseline Value (SD)	References
Cohort Characteristics		
Age (years)	35(8)	[4]
Gender distribution (% male)	21	[4]
Initial CD4 count (/μl), mean (SD)	100(51)	Assumed distribution
	275 (51)	
	425 (51)	
Initial HIV RNA distribution (%), copies/ml		[4] ^a
>100,000	47.0	
30,001–100,000	24.5	
10,001–30,000	15.1	
3,001–10,000	6.6	
500–3,000	2.5	
<500	4.4	
Efficacy of continuous 1st-line NNRTI-based ART and 2nd-line PI-based ART		
HIV RNA <300 copies/ml at 6 months (%)	87	[17]
Monthly virologic failure after 6 months (%)	0.18	[20] ^a
CD4 increase at 12 months (/μl)	152	[20] ^a
Protective effect of ART on severe morbidity (%) ^b	32	[19]
Protective effect of ART on mortality (%)		[19]
CD4 <50/μl	55	
CD4 51–200/μl	91	
CD4 >200/μl	96	
CD4 change during ART interruptions (/μl/month)		[4] ^a
Interruption: months 1–2	–77 (47)	
months 3 and beyond	–7 (7)	
Reintroduction: months 1–2	126 (98)	
months 3 and beyond	9 (18)	
Risk of virologic resistance attributable to each interruption (per 100 person-interruption)	4	[20] ^a
Proportion of patients in STI arm reaching each STI endpoint (%)		[20] ^a
CD4 decline <200/μl during interruption	62	
Severe opportunistic disease event	31	
CD4 decline <200/μl on ART	7	
Costs (2006 USD)		
Cotrimoxazole (\$/month)	2	[12, 15]
1st-line ART (AZT/3TC/EFV) (\$/month) ^c	22	[21]
2nd-line ART (TDF/FTC/LPV/r) (\$/month) ^c	79	[21]
CD4 count monitoring (\$/test)	25	[12, 15]

SD: standard deviation; ART: antiretroviral therapy; NNRTI: non-nucleoside reverse transcriptase inhibitor; STI: structured treatment interruptions; AZT: zidovudine; 3TC: lamivudine; EFV: efavirenz; TDF: tenofovir disoproxil fumarate; FTC: emtricitabine; LPV/r: lopinavir/ritonavir.

^aThese estimates were from primary data sub-analyses that were performed to derive model parameters, and were not published in the cited reference.

^bEffect was found for and applies to all severe opportunistic diseases except for tuberculosis [19].

^cWe used the lowest prices available from generic or brand manufacturers in the 2008 Médecins Sans Frontières report [21].

Table 3

Projected outcomes of STI strategies and continuous ART in Côte d'Ivoire

ART initiation	Strategy (Interruption/ Reintroduction/ μ)	% Eligible for strategy decision	Life Expectancy (months)		Cost (Discounted, 2007 US\$)
			Undiscounted	Discounted	
Initial CD4 $\leq 200/\mu^a$					
Immediate	350/250	77	287	183	19,400
	500/250	60	286	186	18,100
	500/350	60	323	203	21,000
	Continuous ART	---	334	209	23,200
Initial CD4 201–350/μ					
CD4 $<200/\mu$ l or severe OD	350/250	87	285	182	18,400
	500/250	73	282	183	16,800
	500/350	73	327	204	20,400
	700/250	50	322	204	19,400
	700/350	50	338	210	21,200
	700/500	50	346	214	21,500
	Continuous ART	---	345	213	23,300
	350/250	88	291	186	18,700
	500/250	80	285	186	17,000
	500/350	80	337	211	21,500
	700/250	56	332	210	19,900
	700/350	56	350	218	22,300
	700/500	56	361	223	22,600
	Continuous ART	---	361	223	24,800
Initial CD4 351–500/μl					
CD4 $<200/\mu$ l or severe OD	350/250	88	282	181	17,200
	500/250	81	276	180	15,700
	500/350	81	326	204	19,800
	700/250	60	319	202	18,200
	700/350	60	339	211	20,500
	700/500	60	349	215	20,800

ART initiation	Strategy (Interruption/ Reintroduction/ μ)	% Eligible for strategy decision	Life Expectancy (months)		Cost (Discounted, 2007 US\$)
			Undiscounted	Discounted	
CD4 <350/ μ l or severe OD	Continuous ART	---	348	215	22,900
	500/250	87	279	182	15,800
	500/350	87	335	209	20,800
	700/250	66	327	207	18,600
	700/350	66	349	217	21,400
Immediate	700/500	66	362	223	21,800
	Continuous ART	---	362	223	24,200
	500/250	88	281	183	16,100
	500/350	88	338	211	21,500
	700/250	74	324	206	18,400
	700/350	74	351	218	22,000
	700/500	74	366	226	22,500
	Continuous ART	---	368	227	25,200

STI: structured treatment interruptions; OD: opportunistic disease; PY: person-year.

^aWe did not evaluate strategies with interruption CD4 thresholds $\geq 700/\mu$ l in these patients, because the proportion of patients who reached this CD4 count was small (37%), as shown in previous studies [25, 26].