Decrease in sexual risk behaviours after early initiation of antiretroviral therapy: a 24-month prospective study in Côte d'Ivoire.

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Running head: Decrease in sexual risk behaviors after early ART initiation.

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3456 words

ABSTRACT

Introduction: Whether early ART initiation could impact sexual risk behaviors remains to be documented. We aimed to investigate changes in sexual behaviors within the 24 months following an early versus standard ART initiation in HIV-infected adults with high CD4 counts.

Methods: We used data from a prospective behavioral study nested in a randomized controlled trial of early ART (Temprano-ANRS12136). Time trends in sexual behaviors from enrolment in the trial (M0) to 12-months (M12) and 24-months (M24) visits were measured and compared, using Generalized Estimating Equations models, between participants randomly assigned to initiate ART immediately ('early ART') or to defer ART initiation until ongoing WHO starting criteria are met ('standard ART). Sexual behaviors considered were: (i) sexual activity in the past year, (ii) multiple partnerships in the past year, (iii) unprotected sex at last intercourse and (iv) risky sex (unprotected sex with a partner of HIV negative/unknown status) at last intercourse.

Results: Analyses included 1952 participants (early ART, n=975; standard ART, n=977; overall median baseline CD4 counts: 469/mm^3). Among participants with early ART, we found significant decreases between M0 and M24 in sexual activity (Odds Ratio [OR] 0.72, 95% Confidence Interval [95%CI] 0.57-0.92), multiple partnerships (OR 0.57, 95%CI 0.41-0.79), unprotected sex (OR 0.59, 95%CI 0.47-0.75) and risky sex (OR 0.58, 95%CI 0.45-0.76). Among participants with standard ART, time trends in sexual behaviors were not significantly different. These decreases mostly occurred within the 12 months following enrolment in the trial in both groups, and prior to ART initiation in participants with standard ART. For unprotected sex and risky sex, decreases were or tended to be more pronounced among patients reporting that their last sexual partner was non-cohabiting.

Conclusion: In these sub-Saharan adults with high CD4 counts, entry into HIV care, rather than ART initiation, resulted in decreased sexual activity and risky sexual behaviors. We did not observe any evidence of a risk compensation phenomenon associated with early ART initiation. These results illustrate the potential behavioral preventive effect of early entry into care, which goes hand in hand with early ART initiation.

Clinical Trial Number: NCT00495651

INTRODUCTION

With the preventive effect of early antiretroviral therapy (ART), demonstrated by the HPTN052 trial among stable serodiscordant couples (1), the *Test and Treat* prevention strategy appears as a promising way to curb the HIV epidemic in sub-Saharan Africa (2). This strategy consists of universal HIV testing, coupled with immediate ART initiation in those diagnosed HIV positive, regardless of their CD4 count. Estimates of the preventive population-level impact of this strategy are mostly derived from models relying on the hypothesis, yet to be proven, that sexual behaviors would not change after early ART initiation (2,3).

The possibility of risk compensation – increase in risk behaviors as a consequence of decreased perceived risks of HIV burden and/or transmission – may particularly be of concern (4,5). Increase in sexual risk behaviors associated with ART initiation has been previously reported among high-risk groups early in the ART era (6,7), and early models predicted that increases in risk behaviors associated with expanded ART could offset the preventive beneficial impact of ART (8,9). More recently, risk compensation has been suggested to explain the limited impact of ART for reducing HIV incidence in high-resources settings with high rates of HIV testing and treatment coverage (10). However, such an effect of ART on sexual behaviors, if any, may vary depending on the context. According to a recent review of 17 observational studies conducted in resource-limited settings (11), only one study conducted in Côte d'Ivoire reported increased unprotected sex after ART initiation (12). The remaining 16 studies documented decreased levels of sexual risk behaviors associated with ART initiation according to national or international guidelines. These results suggested a beneficial behavioral impact of treatment initiation. They did not settle, though, whether this effect was due to ART itself or to entry into care.

To date, the consequences of ART initiation on sexual behaviors have mostly been studied in the context of standard ART initiation, *i.e.* among patients with a clinically and/or biologically advanced HIV disease requiring treatment initiation as recommended by the World Health Organisation (WHO) (13,14). Health status plays a central role in sexual behaviors, especially in the context of HIV infection (15–17). Therefore, the effect of ART on sexual behaviors could be different when ART is started earlier, *i.e.* in healthier patients potentially more sexually active. In addition, sexual and prevention behaviors, such as condom use or sharing HIV status with partners, have been documented to differ according to the type of partnership (18–21), suggesting that ART initiation may have different consequences on sexual behaviors in the case of stable or occasional partnership.

We used data from the ongoing Temprano ANRS-12136 randomized controlled trial to measure changes in sexual behaviors within the 24 months following early ART initiation and to compare these changes to those observed in patients starting ART according to WHO guidelines. We also investigated differences in sexual behaviors trends according to the type of partnership.

MATERIAL & METHODS

Temprano ANRS 12136 trial

Temprano is a multicenter randomized open-label superiority trial to assess the benefits and risks of initiating ART earlier than currently recommended by WHO, concomitantly or not with a 6-month isoniazide prophylaxis for tuberculosis (IPT). The trial was launched in March 2008 in Abidjan, Côte d'Ivoire, and is still ongoing. It will end in December 2014. The trial protocol was approved by the Côte d'Ivoire national ethics committee and by the institutional review board of the French National Agency for Research on AIDS and viral hepatitis (ANRS, Paris, France). It has been registered on clinicaltrials.gov under the following identifier: NCT00495651.

Between March 2008 and July 2012, patients attending 9 care centers were included in the trial whenever they met the following criteria: signed informed consent; age >18 years; HIV-1 or HIV 1+2 dual seropositivity; no ongoing active tuberculosis; no ongoing pregnancy or breastfeeding; CD4 count <800 cells/mm^3 and no criteria for starting ART according to the most recent WHO guidelines. Participants were randomized into four arms: two "standard ART" arms (arms 1 and 2), in which ART was deferred until patients meet ongoing WHO starting criteria (13,14); and two "early ART" arms (arms 3 and 4), in which ART was initiated immediately on inclusion. In arms 2 and 4, participants received a 6-month IPT, starting at Month-1 visit. Once included, participants were asked to show up for trial scheduled visits at Day-8, Month-1, Month-2, Month-3, and every 3 months thereafter. Standardised questionnaires were used to record baseline and follow-up characteristics. The trial sample included 2076 participants. Each participant will be followed up during 30 months. The main outcome of the trial is the occurrence of a new episode of severe morbidity, defined as AIDS-defining diseases, non-AIDS defining severe bacterial diseases, non-AIDS defining cancers, and any event leading to death.

Socio-behavioral study

The present socio-behavioral study was nested in the Temprano trial. Starting from January 1st 2010, standardized questionnaires were used to record data on participants' sexual behaviors and on the characteristics of their last sexual intercourse, regarding the type of partnership (cohabiting or not), HIV status of the partner (negative, positive, unknown) and condom use. Questionnaires were completed during face-to-face interviews that took place at inclusion, and then at the 12-month and 24-month visits, except for patients in the standard ART arms who initiated ART during the first year of follow-up. The latter completed the questionnaire at the date of ART initiation, and then at 12 months and 24 months after ART initiation. Patients included before January 1st 2010 and who did not have socio-behavioral questionnaires at baseline were interviewed at their 12-month and 24-month visits (after inclusion or ART-initiation) like other patients.

Study outcomes

Four indicators of sexual behaviors were considered: i) sexual activity (*i.e.* at least one sexual intercourse) in the past year; ii) multiple partnership (*i.e*. at least two sexual partners) in the past year;

iii) unprotected sex at last intercourse in the past year; and iv) risky sex (defined as unprotected sex with a partner of HIV negative/unknown status) at last intercourse in the past year.

Statistical analysis

All trial participants having completed a socio-behavioral questionnaire at one or more of the following trial visits were included in the present analysis: i) M0 (inclusion visit), ii) M12 (12±3 months after inclusion), and iii) M24 (24±6 months after inclusion). For all analyses, patients of arms 1 and 2 were pooled in a group referred to as "standard ART" and patients of arms 3 and 4 were pooled in a group referred to as "early ART".

Time trends in the four indicators of sexual behaviors from M0 to M12 and M24 visits were measured and compared between participants with early versus standard ART. To account for multiple observations per individual, marginal Generalized Estimating Equations models (GEE) of logistic regression assuming an exchangeable correlation structure were used. Covariates included in the models were ART group and time period, coded as a 3-level factor in order to allow non-linear changes across time. An interaction term between ART group and time period was added to each model in order to assess differences in time trends according to ART strategy.

In order to investigate different patterns of sexual behaviors according to the type of partnership, we performed interaction tests to assess whether sexual behaviors trends over time differed between sexually active individuals with cohabiting vs. non-cohabiting partners.

Lastly, in order to assess the role on behaviors changes of, respectively, entry into care and ART initiation, we described changes in sexual behaviors before vs. after ART initiation among participants of the standard ART group. For this complementary analysis, we used GEE models including time periods coded as a 4-level factor: i) M0 (inclusion visit), ii) TI (at Treatment Initiation, allowing for a varying time period between M0 and TI for each individual), iii) TI_{+12} (12±3 months after TI), and iv) TI_{+24} (24±6 months after TI).

All analyses were conducted using SAS version 9.3 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Study population

A total of 1952 Temprano participants (standard ART: 977; early ART: 975) completed at least one socio-behavioral questionnaire in due time and were included in the present analysis, accounting for a total of 3364 questionnaires (standard ART: 1653; early ART: 1711). As of March 1st 2013, participants had been followed during a mean time of 25.7 months (Inter Quartile Range, IQR 23.9-30.0), and 57% of participants had completed at least two socio-behavioral questionnaires, with no difference between both ART groups (Table Additional File 1).

Median age at baseline was 35 years and 79% of participants were women. Median baseline CD4 cell count was 469/mm^3 (IQR 379-577). No significant difference in baseline socio-demographic and clinical characteristics was observed between patients on standard vs. early ART (Table 1).

Table 1 : Baseline socio-demographic and clinical characteristics among participants on standard and early antiretroviral therapy (ART). Socio-behavioral study nested in the Temprano Trial (N=1952).

	Standard ART	Early ART	p
Sex			0.31
Men	219 (22.4%)	200 (20.5%)	
Women	758 (77.6%)	775 (79.5%)	
Age	35 [30-42]	35 [30-42]	0.69
Educational level			0.61
None	236 (24.2%)	257 (26.4%)	
Primary	281 (28.7%)	276 (28.3%)	
Secondary	327 (33.5%)	324 (33.2%)	
>Secondary	133 (13.6%)	118 (12.1%)	
Personal source of income			0.35
No	238 (25.4%)	256 (27.3%)	
Yes	700 (74.6%)	682 (72.7%)	
Family status			0.57
Single	417 (42.7%)	414 (42.5%)	
Living in union	460 (47.1%)	447 (45.8%)	
Separated/widowed	100 (10.2%)	114 (11.7%)	
HIV-status disclosure to the partner			0.92
No	467 (52.0%)	467 (52.2%)	
Yes	432 (48.0%)	428 (47.8%)	
WHO clinical stage			0.88
1	632 (64.8%)	622 (63.8%)	
2	252 (25.8%)	262 (26.9%)	
3	86 (8.8%)	87 (8.9%)	
4	6 (0.6%)	4 (0.4%)	
CD4 count cell (/mm3)	470 [375-573]	468 [384-580]	0.48

Patients in the standard ART group deferred ART initiation until ongoing WHO starting criteria were met, whereas patients in the early ART group initiated ART immediately on inclusion in the trial.
Counts (%) and Chi2 p-values are presented for categorical measures. Percent are computed as a fraction of non-missing observations. Medians (interquartile ranges) and t-test p-values are presented for quantitative measures.

Sexual behaviors within the 24 months following inclusion

The frequency of being sexually active decreased from 79.9% at M0 to 72.6% at M24 among participants on early ART and from 75.9% to 69.8% among participants on standard ART (Figure 1.a).

During the same period, the frequency of reporting multiple partnerships decreased from 14.4% to 8.7% in the early ART group and from 12.8% to 7.6% in the standard ART group (Figure 1.b). Baseline frequencies of reporting unprotected sex were 40.7% on early ART and 38.1% on standard ART; they decreased to 27.3% and 23.9%, respectively, at M24 (Figure 1.c). The frequency of reporting risky sex decreased from 26.8% at M0 to 17.3% at M24 among participants on early ART and from 28.4% at M0 to 15.5% at M24 among participants on standard ART (Figure 1.d).

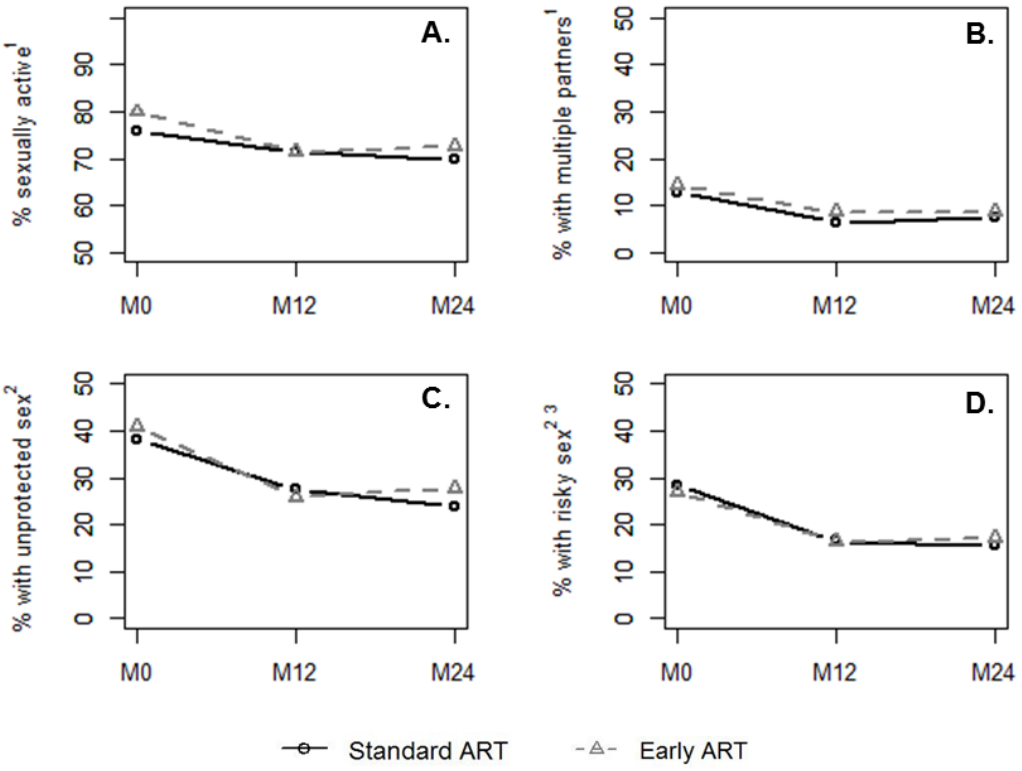

Figure 1: Sexual behaviors reported at inclusion (M0), 12-month visit (M12) and 24-month visit (M24) among participants on standard and early antiretroviral therapy (ART). Socio-behavioral study nested in the Temprano Trial (N=1952).
Patients in the standard ART group deferred ART initiation until ongoing WHO starting criteria were met, whereas patients in the early ART group initiated ART immediately on inclusion in the trial.
[1] In the past year.
[2] At last intercourse in the past year.
[3] Defined as an unprotected intercourse with a partner of negative/unknown HIV status.

As shown in Table 2, frequencies of being sexually active, reporting multiple partnerships, unprotected sex and risky sex significantly decreased between M0 and M12 in both ART groups (each Odds Ratio, $OR_{M12\ vs.\ M0}<1$ with $p<0.01$); with the exception of the decrease in sexual activity in the standard ART group, which was borderline significant ($OR_{M12\ vs.\ M0}$ 0.80; 95% Confidence Interval [95%CI] 0.64-1.01]). Subsequently, for the four indicators, the frequencies did not significantly change between M12 and M24 (each $p>0.05$).

The interaction term between randomization group and time was not significant for the four sexual behaviors indicators (each p>0.15), suggesting that the observed time trends between M0 and M24 were not significantly different between both ART strategies.

A complementary analysis was conducted, restricting the GEE analysis to the sexually active population first, and then to the population reporting no condom use at last intercourse. In both cases, the decrease observed between M0 and M12 in risky sex remained significant (data not shown).

Differences according to the type of partnership

Among sexually active participants, the overall proportion reporting that their last partner was non-cohabiting was 39.9% at M0; 40.1% at M12; and 42.7% at M24. These proportions were higher among women than men (overall, 44.8% vs. 28.5%, $p<10^{-3}$).

Regardless of ART strategy and type of partnership, frequencies of reporting multiple partnership, unprotected sex and risky sex decreased between M0 and M12 (Table 3). For unprotected sex and risky sex, these decreases were or tended to be more pronounced among participants reporting a non-cohabiting partner at last intercourse ($OR_{M12\ vs.\ M0}$ between 0.36 and 0.42) than among those reporting a cohabiting partner ($OR_{M12\ vs.\ M0}$ between 0.60 and 0.77). This differential decrease was not observed for multiple partnerships.

Subsequently, frequencies of multiple partnership, unprotected sex and risky sex generally did not significantly change between M12 and M24, regardless of ART group or partnership. The only exception was a significant decrease between M12 and M24 in the frequency of unprotected sex among participant of the standard ART group reporting a cohabiting partner at last intercourse.

Sexual behaviors before/after ART initiation among participants on standard ART

The complementary analysis involved 802 participants of the standard ART group who completed a socio-behavioral questionnaire at M0, at treatment initiation (TI), at 12 months after TI (TI_{+12}) or at 24 months after TI (TI_{+24}), representing a total of 1455 questionnaires. Among them, 492 initiated ART, with a median time of 14.0 months (IQR 8.0-20.1) between enrollment and treatment initiation.

Among this group of participants, the frequency of being sexually active did not significantly change over time between M0 and TI_{+24} (Table 4). In contrast, frequencies of reporting multiple partnership, unprotected sex and risky sex significantly decreased between M0 and treatment initiation (multiple partnership: $OR_{TI\ vs.\ M0}$ 0.41, 95%CI 0.26-0.64; unprotected sex: $OR_{TI\ vs.\ M0}$ 0.65, 95%CI 0.49-0.85; risky sex: $OR_{TI\ vs.\ M0}$ 0.62, 95%CI 0.45-0.84). Subsequently, the frequencies of these three indicators did not significantly change over time within the 24 months following treatment initiation (each p>0.15).

Table 2: Time trends in sexual behaviors indicators within the 24 months following enrollment in the trial among participants on standard and early antiretroviral therapy (ART). Socio-behavioral study nested in the Temprano Trial (N=1952).

	Standard ART				Early ART				Interaction p [3]
t_1 to t_2	**% change[1]**	**OR(t_2 vs. t_1)[2]**	**95%CI**	**p**	**% change[1]**	**OR(t_2 vs. t_1)[2]**	**95%CI**	**p**	
Sexual activity[4]									**0.61**
M0 to M24	-6.1	0.76	[0.59 ; 0.96]	0.022	-7.3	0.72	[0.57 ; 0.92]	0.008	
M0 to M12	-4.4	0.80	[0.64 ; 1.01]	0.062	-8.5	0.70	[0.57 ; 0.87]	0.002	
M12 to M24	-1.7	0.94	[0.79 ; 1.11]	0.45	+1.2	1.03	[0.87 ; 1.22]	0.77	
Multiple partnership[4]									**0.64**
M0 to M24	-5.2	0.55	[0.38 ; 0.80]	0.002	-5.7	0.57	[0.41 ; 0.79]	$<10^{-3}$	
M0 to M12	-6.4	0.49	[0.34 ; 0.70]	$<10^{-3}$	-5.8	0.60	[0.44 ; 0.83]	0.002	
M12 to M24	+1.2	1.13	[0.78 ; 1.64]	0.48	+0.1	0.94	[0.69 ; 1.27]	0.63	
Unprotected sex[5]									**0.16**
M0 to M24	-14.2	0.50	[0.39 ; 0.64]	$<10^{-3}$	-13.4	0.59	[0.47 ; 0.75]	$<10^{-3}$	
M0 to M12	-10.5	0.61	[0.48 ; 0.78]	$<10^{-3}$	-14.7	0.55	[0.43 ; 0.70]	$<10^{-3}$	
M12 to M24	-3.7	0.83	[0.68 ; 1.01]	0.06	+1.3	1.09	[0.89 ; 1.32]	0.41	
Risky sex[5,6]									**0.56**
M0 to M24	-12.9	0.48	[0.36 ; 0.63]	$<10^{-3}$	-9.5	0.58	[0.45 ; 0.76]	$<10^{-3}$	
M0 to M12	-11.8	0.52	[0.39 ; 0.69]	$<10^{-3}$	-10.4	0.55	[0.42 ; 0.72]	$<10^{-3}$	
M12 to M24	-1.1	0.93	[0.74 ; 1.17]	0.52	+0.9	1.06	[0.84 ; 1.34]	0.64	

Patients in the standard ART group deferred ART initiation until ongoing WHO starting criteria were met, whereas patients in the early ART group initiated ART immediately on inclusion in the trial.

[1] Change in percentage points between t_1 and t_2.

[2] Odds Ratio of reporting the corresponding sexual behavior at t_2 as compared to t_1 (logistic regression model with Generalized Estimating Equations).

[3] P-value of the overall likelihood-ratio test for interaction between ART group and time (for the whole M0-M24 period).

[4] In the past year.

[5] At last intercourse in the past year.

[6] Defined as an unprotected intercourse with a partner of negative/unknown HIV status.

M0: at inclusion in the trial; M12: 12 months after inclusion; M24: 24 months after inclusion; OR: Odds Ration: CI: Confidence Interval.

Table 3: Time trends in sexual behaviors indicators within the 24 months following enrollment in the trial among participants on standard and early antiretroviral therapy (ART), by type of partnership. Socio-behavioral study nested in the Temprano Trial (N=1642 sexually active participants).

	Standard ART							Early ART						
	Cohabiting partner			Non-cohabiting partner			Inter-action p [2]	Cohabiting partner			Non-cohabiting partner			Inter-action p [2]
	OR(t_2 vs. t_1)[1]	95%CI	p	OR(t_2 vs. t_1)[1]	95%CI	p		OR(t_2 vs. t_1)[1]	95%CI	p	OR(t_2 vs. t_1)[1]	95%CI	p	
Multiple partnership[3]							0.92							0.48
M0 to M12	0.44	[0.23 ; 0.84]	0.013	0.52	[0.31 ; 0.87]	0.012		0.59	[0.36 ; 0.96]	0.033	0.64	[0.39 ; 1.05]	0.07	
M12 to M24	1.22	[0.64 ; 2.32]	0.55	1.16	[0.69 ; 1.94]	0.57		0.70	[0.39 ; 1.23]	0.21	0.98	[0.62 ; 1.54]	0.93	
Unprotected sex[4]							0.038							0.15
M0 to M12	0.77	[0.54 ; 1.10]	0.15	0.41	[0.26 ; 0.64]	<.001		0.68	[0.48 ; 0.95]	0.023	0.41	[0.26 ; 0.66]	$<10^{-3}$	
M12 to M24	0.68	[0.52 ; 0.89]	<.001	1.18	[0.79 ; 1.77]	0.43		1.11	[0.84 ; 1.46]	0.48	1.10	[0.72 ; 1.66]	0.67	
Risky sex[4,5]							0.27							0.048
M0 to M12	0.60	[0.42 ; 0.86]	0.006	0.42	[0.26 ; 0.68]	<.001		0.77	[0.56 ; 1.07]	0.12	0.36	[0.22 ; 0.60]	$<10^{-3}$	
M12 to M24	0.78	[0.59 ; 1.03]	0.08	1.16	[0.76 ; 1.78]	0.48		0.94	[0.69 ; 1.28]	0.68	1.33	[0.85 ; 2.09]	0.21	

Patients in the standard ART group deferred ART initiation until ongoing WHO starting criteria were met, whereas patients in the early ART group initiated ART immediately on inclusion in the trial.

[1] Odds Ratio of reporting the corresponding sexual behavior at t_2 as compared to t_1 (logistic regression model with Generalized Estimating Equations).

[2] P-value of the overall likelihood-ratio test for interaction between type of partnership and time (for the whole M0-M24 period).

[3] In the past year.

[4] At last intercourse in the past year.

[5] Defined as an unprotected intercourse with a partner of negative/unknown HIV status.

M0: at inclusion in the trial; M12: 12 months after inclusion; M24: 24 months after inclusion, OR: Odds Ration: CI: Confidence Interval.

Table 4: Time trends in sexual behaviors indicators before and after standard antiretroviral therapy (ART) initiation. Socio-behavioral study nested in the Temprano Trial (N=802).

	Sexual activity [1]			Multiple partnership [1]			Unprotected sex [2]			Risky sex [2.3]		
	OR(t_2 vs. t_1) [4]	95%CI	p	OR(t_2 vs. t_1) [4]	95%CI	p	OR($t_2$vs. t_1) [4]	95%CI	p	OR($t_2$vs. t_1) [4]	95%CI	p
M0 to TI	0.91	[0.70 ; 1.19]	0.50	0.41	[0.26 ; 0.64]	<10-3	0.65	[0.49 ; 0.85]	0.002	0.62	[0.45 ; 0.84]	0.002
TI to TI_{+12}	0.96	[0.76 ; 1.21]	0.73	0.98	[0.55 ; 1.72]	0.93	1.08	[0.84 ; 1.37]	0.56	0.91	[0.68 ; 1.21]	0.52
TI_{+12} to TI_{+24}	0.96	[0.78 ; 1.18]	0.68	0.65	[0.34 ; 1.23]	0.19	0.86	[0.70 ; 1.09]	0.22	0.88	[0.67 ; 1.15]	0.35

Patients in the standard ART group deferred ART initiation until ongoing WHO starting criteria were met.

[1] In the past year.

[2] At last intercourse in the past year.

[3] Defined as an unprotected intercourse with a partner of negative/unknown HIV status.

[4] Odds Ratio of reporting the corresponding sexual behavior at t_2 as compared to t_1 (logistic regression model with Generalized Estimating Equations).

M0: at inclusion in the trial; TI: at treatment initiation; TI_{+12} :12 months after ART initiation; TI_{+24} :24 months after ART initiation; OR: Odds Ration: CI: Confidence Interval.

DISCUSSION

In this study nested in an ongoing randomized controlled trial of early ART, we found decreases in several reported sexual behaviors in the 24 months following inclusion. These decreases mostly occurred within the 12 months following enrolment in the trial in both groups, and prior to ART initiation in participants with standard ART. They did not differ between participants having initiated ART early and those having deferred ART according to WHO recommendations, suggesting that such time trends might be a result of early entry into care rather than ART initiation (whether early or not). In addition, regardless of ART strategy, decreases in two sexual risk behaviors indicators, unprotected sex and risky sex, tended to be more pronounced for patients reporting non-cohabiting partners as compared to those with cohabiting partners.

Sexual behaviors in the context of HIV care have been previously investigated in Côte d'Ivoire. Three studies conducted among HIV-infected patients, both treated and untreated, documented levels of sexual activity in the past 6 months ranging approximately from 50 to 65% (12,22,23). The higher level of sexual activity (71%) during the past year reported here may be explained by a longer recall period. It may also be related to a better health status among our study population composed of patients recruited at an early stage of the HIV infection. These previous studies also reported levels of unprotection, as measured through inconsistent condom use (*i.e.* at least one unprotected intercourse during the previous six months) ranging from 20 to 30% when recorded among the entire population (12,22,23). This is consistent with the 25% participants who reported unprotected sex at last intercourse in our study.

Four indicators of sexual behaviors were used in this study. Among these, risky sex (*i.e.* unprotected sex with a partner of HIV negative/unknown status) may be considered as the best proxy of the partner's exposure to HIV infection. Among both ART groups, the OR of reporting risky sex at last intercourse at M24, as compared to M0, was close to 0.5. This approximately represents, when accounting for the prevalence of risky sex, a 40% decrease at the population level (24). This indicator integrates different components: sexual activity, condom use and partner's HIV status. Complementary analyses suggested that this time trend reflected not only a decrease in overall sexual activity, but also an increase in condom use and in knowledge of partner's HIV status over time. Decrease in sexual activity, number of sexual partners or unprotected intercourses have previously been reported in the context of biomedical prevention trials (25–27). At the community level, a substantial increase in condom use has also been recently documented in South Africa during ART coverage scale-up (28).

For each time step we considered, sexual behavior levels were not different between the two ART groups. These observations might challenge the results of several literature reviews, which pointed out decreased sexual risk behaviors associated with ART (11,29–31). However, these previous studies relied on comparison between treated vs. pre-ART patients in a context where routine contacts with the care system are generally infrequent for patients not eligible to ART (32).It

has been previously suggested that the behavioral effect of ART may be due to frequent contact with medical care, rather than to ART itself, since attendance to care provides counseling and psychosocial support (23,33). The similar decreases in risk behaviors we observed among both ART groups, as well as the absence of additional decrease after treatment initiation in the standard ART group support this hypothesis. Actually, the Temprano protocol provided the same frequency of medical encounters in both ART groups. Besides, the protocol did not include any additional intervention to reduce risk behaviors apart from routine clinic-based HIV counseling. Our results thus suggest that, as compared to an entry into standard care at early stage of the HIV-infection, early ART did not differently impact sexual behaviors.

The dynamics of the changes we document here is consistent with previous results. A previous study conducted in Uganda indicated a dramatic decrease in unprotected sex at last intercourse during the first year following standard ART initiation, and then a stabilized level during the following two years (34). The changes in sexual behaviors we described seem to occur immediately after inclusion in the trial. These changes might integrate modifications in sexual behaviors following the announcement of the HIV diagnosis (35,36), which occurred potentially recently before enrollment in the trial among our study population selected to have high levels of CD4. Subsequently, after 12 months of follow-up, we did not observe further decrease in our indicators of sexual behaviors. Neither did we observe any "prevention fatigue" (*i.e.* a decrease in preventive behaviors over time) as it has been previously observed among high-risk groups (37). However, our results were obtained within a relatively short follow-up time (24 months). Further studies are needed to measure long term changes in sexual behaviors after early entry into care.

When taking into account the different types of partnerships, our results presented an interesting feature: decreases in sexual risk behaviors were more pronounced among patients reporting that their last sexual partner was non-cohabiting vs. cohabiting. This differential decrease may reflect a lower level of condom use among cohabiting than non-cohabiting relationships, or respectively spousal and non-spousal, as it has been observed in other African settings (19,20). It may also reflect the fact that it is more difficult to modify sexual behaviors once they are already fixed among a couple. In both cases, these results underline the need of specific prevention messages oriented to established couples.

Our results provide some insights into the issue of risk compensation. We did not observe increases in risk behaviors associated with an intervention conferring a strong preventive effect against HIV transmission. Actually, levels of risk behaviors were similar among those receiving or not the intervention, and, overall, they appeared to decrease after inclusion in the trial. However, those results must be considered with caution. Temprano is a clinical trial which primary objective was to measure the individual rather than collective benefits and risks of early ART. Thus, before the implementation of the 2012 WHO guidelines (38), specific information about the preventive benefits of ART was not delivered as part of the pre-inclusion interview. Participants may however have received this information outside the trial, for instance through patients associations, after the publication and media exposure of the HPTN052 trial results (1).

To our knowledge, this study is the first one to prospectively document detailed sexual behaviors after early ART initiation. It has the advantage to rely on a large dataset collected after randomization of the intervention. We acknowledge though that our results may be subject to some bias. This study relies on self-reported sexual behaviors, which may have been under-reported because of social desirability. However, in order to prevent such a bias, interviewers were trained to administer questionnaires in a non-judgmental way and interviews were conducted confidentially in private rooms. In addition, a literature meta-analysis on the topic showed that face-to-face interview does not always yield to lower estimates of sexual risk behaviors as compared to alternative interviewing tools (39). Actually, we reported higher levels of sexual activity than previous studies conducted among HIV-positive patients in Côte d'Ivoire (12,22,23). This suggest that our results are unlikely to be explained by this sole bias. Given the design of this study, it is difficult to disentangle the effect of entry into care from that of enrollment in the trial. However, Temprano is not a prevention trial, but a clinical trial in which only conventional HIV counselling as provided in routine HIV care is offered. Besides, our sample was made of patients recruited in nine clinical centers which reflect the diversity of clinical settings existing in Abidjan (hospitals, private clinics, NGO, and primary care center). In each participating center, all eligible patients were systematically approached to participate in the trial. The total refusal rate was quite low (16%), indicating a limited selection bias.

CONCLUSION

Via its biological effect, early ART reduces the risk of transmitting HIV to the sexual partner, which has been documented among the same population of patients (40). The present study did not document any evidence of a risk compensation phenomenon associated with early ART initiation. Our results rather suggest that early entry into care, which goes hand in hand with early ART initiation, also carries a substantial behavioral preventive effect. This underlines that, concurrently with the prevention potential of ART, conventional interventions targeting behaviors have still a role to play within combined prevention strategies.

COMPETING INTERESTS

The authors do not have any commercial or other associations that constitute competing interests.

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AUTHOR'S CONTRIBUTIONS

RM, CD, ADL, SE, and XA designed the trial. RM, CD, JBN, JLC, AB, and XA collected the data. KJ, DG, FL, and RDS conceived and designed the analysis. KJ conducted the analysis. KJ, FL and RDS wrote the first draft of the manuscript. DG, RM, CD, ADL, JBN, JLC, AB, SE and XA contributed to the manuscript's review and edition.

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ADDITIONAL FILE

Additional File 1 : Socio-behavioral questionnaires completion among participants on standard and early antiretroviral therapy (ART). Socio-behavioral study nested in the Temprano Trial (N=1952).

		Standard ART	Early ART	p
Number of completed questionnaires per participant				0.15
	1	444 (45.5%)	404 (41.4%)	
	2	390 (39.9%)	406 (41.6%)	
	3	143 (14.6%)	165 (16.9%)	
Questionnaires' timing of completion				0.79
	M0	423 (25.6%)	437 (25.5%)	
	M12	547 (33.1%)	584 (35.3%)	
	M24	683 (41.3%)	690 (40.3%)	

Patients in the standard ART group deferred ART initiation until ongoing WHO starting criteria were met, whereas patients in the early ART group initiated ART immediately on inclusion in the trial.
M0: at inclusion in the trial; M12: 12 months after inclusion; M24: 24 months after inclusion.