Effect of early antiretroviral therapy on sexual behaviors and HIV-1 transmission risk in adults with diverseheterosexual partnership statusesin Côte d'Ivoire

Running head: Effect of early ART on sexual behaviors

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Background: The effect of early antiretroviral therapy (ART) on sexual behaviors and HIV-1 transmission risk has not been documented beyond the specific population of stable serodiscordant couples.

Methods: Based on a behavioralstudy nested in a randomized controlled trial (Temprano-ANRS12136) of early ART, we compared proportions of risky sex (unprotected sex with a partner of negative/unknown HIVstatus) reported 12 months after inclusion between participants randomized to initiate ART immediately ('early ART') or according to WHO criteria ('standard ART'). Group-specific HIV-transmission rates were estimated based on sexual behaviors and viral load-specific per-act HIV-1 transmission probabilities. Their ratio was computed to estimate the protective effect of early ART.

Results: Among 957 participants (baseline CD4: 478/mm^3), 46.0% reported sexual activity in the past month, 41.5% of them with non-cohabiting partners. Proportion of risky sex was10.0%*vs.* 12.8%, respectively, in participants on early *vs.* standard ART (p=0.17). Accounting for sexual behaviors and viral load, the estimated protective effect of early ART was 90% (95%CI 81-95%).

Conclusion: Twelve months after inclusion,patients on early and standard ART reported similar sexual behaviors. Early ART decreased the estimated risk of HIV transmission by 90%, suggestinga major prevention benefit among both stable and casual partners.

Key-words: HIV prevention; antiretroviral treatment; sexual behaviors; HIV-1 sexual transmission;Treatment as Prevention; epidemiology; sub-Saharan Africa

Introduction

By controlling viral replication, antiretroviral therapy (ART) reduces the infectivity of HIV-positive patients, with some evidence that patients with an undetectableviral load (VL)havea negligible HIV-transmission risk [1,2]. In 2011, the HPTN052 trial demonstrated that initiating ART between 350-550 CD4, *i.e.* earlier than recommended by the World Health Organization (WHO) guidelines, had a 96% preventive effect against HIV transmission among stable serodiscordant couples [3].This evidence strengthened the Treatment as Prevention (TasP) concept, under which providing ART to all HIV infected patients, regardless oftheir CD4 count, might decrease HIV transmission among the general population in such an extent that it would curtail the HIV pandemic[4,5].Results of TasP randomized controlled trials are not expected before several years [6]. Meanwhile, there are still questions regarding factors that might impact the effect of early ART in the general population and make this effect different from that observed in the very specific group of stable serodiscordant couples.

Among these factors, the impact of early ART on risky sexual behaviors is one of major concern. In the first years of the highly active ART era, increased risky sexual behaviors associated with ART were reported among high-risk groups [7,8]. Risk compensation related to decrease in perception of HIV transmission risk and severity of HIV infection may potentiallyoffset the protective effect of early ART [9,10]. Nevertheless, a recent review of observational studies conducted in developing countries rather suggested a decrease in risky sexual behaviors after ART initiation [11]. However, such studies may be subject to confounding. In addition, only few of themwere prospective [12], and all were conducted in thecontext of standard ART initiation [11,13]. Starting ART earlier,in healthy patients, may impact on sexual behaviors differently. Updating results about this issue, especially in the current context of early ART initiation, is thus needed[14].

Evidence obtained so far has resulted in WHO recommendations of early ART for prevention specifically for the population of serodiscordant couples[15].Nevertheless, according to a recent estimation, only less than a third of new HIV transmissions in sub-Saharan Africa occurs among these couples [16]. This suggests that programs targeting solely stable serodiscordant couples may lack to prevent the majority of new infections. Estimating the preventive effect of early ART beyond the population of stable serodiscordant couples is thus of great interest for scaling-up effective prevention strategies.

Relying on data from the ongoing Temprano-ANRS12136randomized controlled trial, we aimed to measure the impact of early ART initiation on sexual behaviors and to estimate itsprotective effect among a West African adult population reporting diverseheterosexual partnership status (serodiscordant or concordant, stable or casual).

MATERIAL & METHODS

Temprano-ANRS12136 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. The trial protocol was approved by the ethics committee of the Ministry of Health of Côte d'Ivoire 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 in Abidjan were included in the trial whenever they met the following criteria: signed informed consent; age>18 years; HIV-1 or HIV 1+2 dual infection; 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 (arm 1 and 2), in which ART wasdelayeduntil patients meet ongoing WHO starting criteria[17,18]; and two "early ART" arms(arm 3 and 4), in which ART was initiated immediately on inclusion. In arm 2 and arm 4, participants received a 6-month IPT, starting at the Month-1 visit and stopping at the Month-7 visit. Once included, participants were asked to show up for trial scheduled visits every 3 months. CD4 count and plasma HIV-1 RNA (real-time PCR, Taq Man technology Abi Prism 7000, Applied Biosystems, detectability 300 copies/mL) were measured every 6 months.Each participant was to be followed during 30 months. The main outcome of the trial is the occurrence of a new episode of severe morbidityand any event leading to death.

Socio-behavioral study

The present socio-behavioral study was nested in the Temprano trial. All participants included in Temprano between January 1st 2009 and September 1st 2011 were eligible for the study. A standardized questionnaire was used to collect information on sexual behaviors. Participants completed this questionnaire face-to-face at the 12-month visit (M12).

Study outcomes

Sexual behaviors of interest included sexual activity and multiple partnerships in the past year, and characteristics of the last sexual intercourseincludingdate (occurred in the past month/past year), type of partnership (cohabiting or not) and partner's HIV status (unknown/negative/positive).

Risky sex at last sexual intercourse in the past month was defined as an unprotected intercourse with a partner of HIV negative/unknown status. Partner's exposure to HIV infection was defined as risky sex associated with a measure of VL≥300 copies/mm^3 at the time of the intercourse, *i.e.* within a period ranging from 30 days before to 7 days after thedate of completion of the socio-behavioral questionnaire.

For each sexually active participant, a HIVtransmission risk for the lastintercourse in the past month was calculated based onreported partner's HIV status, condom use and VL measured at the time of the intercourse. Per-coital-act VL-specific probabilities of transmission were derived from a seroconversion study of HIV-discordant couples in eastern and southern Africa [19], using the following formula:

$$p = 1 - e^{-e^{(-7.257 + 1.070 * (Log(VL) - 4) - 0.025 * (age - 35))}}$$

where *p* is the per-coital probability of HIV transmission (J.P. Hughes, personal communication).

Patients with undetectable VL were assigned a null transmission risk [2]. We attributed a 78% transmission risk reduction if condom was reported, and, for female participants, we considered each last sexual male partner as circumcised (96% of men actually are in Côte d'Ivoire [20]) and thus applied a 53% transmission risk reduction [19]. Partners with unknown HIV status were considered as HIV-uninfected. For a partner reported as HIV-positive, transmission risk was set to zero.

We estimated HIV-transmission rates at last sexual intercourse in the past month for both ART strategies by computing means of individual transmission risks, expressed per 10,000 sexually active individuals.

In order to estimate transmission rates in the whole studied population and not only among sexually active persons, we computed an additional estimation including participants sexually inactive in the past month, attributing them a null individual transmission risk.

Statistical analysis

Participants included in the Temprano trial between January 1st 2009 and September 1st 2011 were included in the analysisprovided they completed the 12-monthsocio-behavioral questionnaire in due time (±3 months).

Analyses were conducted in intention to treat. Sexual behaviors of interest were compared between early ART and standard ART strategies using Chi-2 tests. The protective effect of the early ART strategy on HIV-transmission risk was based on the ratio of transmission rates.

To assess the robustness of our estimates, we conducted a range of sensitivity analyses, considering: (i) only participants with baseline CD4>350/mm^3; (ii) only those engaged in a cohabiting serodiscordant relationship; (iii) a non-null transmission probability for those having a VL<300 copies/mm^3[21]; (iv) an alternative dataset for VL-specific transmissions probabilities[22]; (v) a probability of 0.4 to be HIV-positive for a sexual partner with unknown serostatus; (vi) all participants as having had a last unprotected intercourse with a HIV-negative partner.

All analyses were conducted using SAS version 9.3 (SAS Institute, Cary, North Carolina, USA). We computed 95% Confidence Intervals for expected transmission rates and protective effect of early ART using bootstrap (10,000 re-sampling).

RESULTS

Study population

Among the 1172participants included in the Temprano trial between 1st January 2009 and 1st September 2011, 957 (81.7%) were included in the analyses(standard ART: 467; early ART: 490). Participants on early and standard ART attended a similar mean number of trial medical visitsbetween enrollment and 12 months (standard ART: 5.9; early ART: 6.2).

The remaining 215 were excluded (standard ART: 123*vs.* early ART: 92; p=0.03) for the following reasons:deathwithin the first 12 months (6*vs.* 9, respectively; p=0.42); not showing up for 12-month visit (17*vs.*38, respectively; p=0.003);12-month socio-behavioral questionnaire not or untimely completed (standard ART: 93, of which 59 had initiated ARTbefore the 12-month visit; early ART: 30; p=0.02).

Participants included in the study did not differ from those excluded regarding socio-demographic characteristics, except for schooling (at least secondary level: included 47.1%, excluded 38.1%; p=0.02).

Among the 957 participants, a large majority (80.4%) were women. At baseline, median age was 35 years and 442 participants (46.2%) were living in union. Neither baseline socio-demographic and clinical characteristics (Table 1) nor baseline VL distributions (Wilcoxon rank-sum test: 0.53; Figure 1a)significantly differed between participants on early *vs.* standard ART.

At the 12-month visit, 70 (15.0%) patients in standard ART had initiated ART (median duration between inclusion and ART initiation: 9.5 months). Overall, VL measured at 12-month was available for 427 (91.4%) patients on standard ART and 468 (95.5%) on early ART.As expected, due to the difference in ART coverage, the percentage of patients with undetectable VL was significantly lower in those on standard ART *vs.* early ART (Wilcoxon rank-sum test: $p<10^{-3}$; Figure 1b).

Sexual Behaviors, Risky Sex and Partner's Exposure to HIV infection at 12-month visit

Sexual behaviors in the past 12 months are presented in Table 2. No significant difference was observed between patients on standard *vs.* early ART in the proportions of sexual activity (standard ART: 71.7% *vs.* early ART: 69.8%; p=0.51) and multiple partnerships (6.2% *vs.* 9.0%, respectively; p=0.11) in the past year. Among sexually active participants, 41.2% *vs.* 41.8%, respectively, reported they were not cohabiting with their last sexual partner (p=0.87). Overall, the last sexual partner was reported to be HIV-uninfected by 26.6% *vs.* 22.8% of sexually active participants, respectively; and to have an unknown HIV-status by 43.9% *vs.* 47.7%, respectively (p=0.47).

Characteristics of the last intercourse in the past month are presented in Table 3. Participants on standard vs. early ART did not significantly differ as regard to sexual activity in the past month and condom use. Risky sex was reported by 12.8% of participants in standard ART *vs.* 10.0% in early ART

(p=0.54). When taking into account last available VL, the proportions of participants exposing their partner to HIV infection were 10.7% *vs.* 2.4%, respectively (p<0.001).

Estimated HIV-transmission rates at 12-month visit

Figure 2a shows the estimated HIV-transmission rates per 10,000 sexually active persons at last sexual intercourse in the past month, based on risk behaviors and VL data, for both ART strategies. Theestimated transmission ratewas 4.0/10,000 (95% Confidence Interval, 95%CI: 3.0-5.0) among those onstandard ARTand 0.5/10,000 (95%CI: 0.2-0.8) among those on early ART. The corresponding estimated protective effect of early ART against HIV transmission was 89% (95%CI: 79-95%).When including all participants in the computations (Figure 2b), the estimatedtransmission ratewas 1.9/10,000 (95%CI: 1.4-2.4) in those on standard ART*vs.*0.2/10,000(95%CI: 0.1-0.3) in those on early ART, representing a protective effect of 90% (95%CI: 81-95%).

Results of sensitivity analyses are presented in Table 4. Whereas estimates of transmission rates varied substantially across scenarios, the estimated protective effect of early ART remained robust (ranging from 84 to 90%).

Relying on the estimated distribution of coital frequency previously reported among serodiscordant couples [22], we assumed a monthly number of 8 sexual intercourses for those sexually active in the past month (zerofor those inactive) and extrapolated the characteristics reported for the last intercourse to all intercourses. Based on this assumption and on our estimate of transmission rates at last sexual intercourse calculated in the whole studied population, we estimated that early ART, compared to a standard ARTstrategy, could prevent 13.4 (95%CI: 9.4-17.7) infections for 10,000 patients during the 12^{th} month following early ART initiation. By extrapolating this monthly number to the whole M0-M12 period, we estimated that early ART could prevent 161 (95%CI: 113-212) infections for 10,000 patients in their first year of treatment (based on estimated incidence rate of 18.7 infections /10,000 persons-years [PY] in early ART and 179.0/10,000 PY in standard ART).

DISCUSSION

In this study, nested in an ongoing randomized trial of early ART, patients who started ARTat high CD4 counts and those who delayed ART initiation until WHO criteria are met declared similar

sexual behaviors at 12 months. Early ART was estimated to decrease by 90% the risk of HIV transmission to partners. This estimated risk reduction, which accounted for well-identified determinants of HIV transmission including VL, sexual partnership, condom use and circumcision[19], was mainly attributable to differences in VL levels between patients on early *vs.* standard ART.In contrast with previous studies that demonstrated the protective effect of ART among the sole serodiscordant stable couples, these estimates were derived from a diverse population with a wide range of partnerships and of partners' HIV status. More than half of our patients were not in a cohabiting relationship, and about two thirds of those sexually active reported a last partner with HIV-negative or unknown status.

The first very original finding of this study is about sexual behaviors in patients on early ART, which were comparable to those reported by patients on standard ART 12 months after inclusion. The sample size was large enough to allow the detection of a 5% difference (from 5% to 10%) between both ART strategies with a power of 0.95. Overall proportions of sexual activity in the past year (71%) and unprotection at last intercourse (25.4%) were consistent with figures previously reported inCôte d'Ivoirein patients treated at late stages of HIV infection [23–25]. To our knowledge, no data on sexual behaviors in the context of early ART has been publishedto date.

According to a recent review conducted in developing countries, decrease in unprotected sex was observed in 16 over 17 observational studies among patients on standard initiated treatment[11]. Such a decline in unprotected sex associated with ART may be explained by the multiple medical encounters that treated patients have with the care system, which ensures a high level of prevention counseling and psychosocial support [25,26]. In routine, contacts with the care system are often rare for patients non-eligible for ART [27].In our study, participants inearly and standard ART strategiesboth had a high frequency of contact with medical care, which may explain comparability in self-reported sexual behaviors. Because data reported in the standard ART initiation context show that sexual behaviors changes may occur over a long time period [28], sexual behaviors changes in relation with early ART initiation deserve to be further assessed on the long term.

We used three different indicators to estimate HIV-transmission risk and its reduction. First, the proportion of last sexual intercourses exposing the partner to HIV infection based on the plasma VL level. This proportion was significantlylower among participantson early *vs.* standard ART**.**Proportions of unprotected intercourses with serodiscordant partners regardless of VL level were

not significantly different between both ART strategies. This suggests that the protective effect of early ART compared to a standard strategy principally lies on the biological effect of the treatment on viral replication rather than on a combination of biological and behavioral effect, as suggested by others[11].

Our second estimate of HIV-transmission risk was the expected number of transmissions at last intercourse in the past month, combining sexual behavior (condom use, partner's HIV status, and circumcision), exact VL values and HIV-1 transmission probabilities from the literature[19]. This methodology has been recently used and showed consistent results as compared to a seroconversion study [29]. Based on it, we estimated a protective effect of early ART of 90%. The magnitude of the protective effect we found was remarkably consistent across populations considered in the analysis, changes in our assumptions and variations in the parameters (Table 4), arguing for the robustness of our estimate. Moreover, this protective effect was close to those estimated in the HPTN052 study (96%) [3] and in a systematic review of prospective studies among discordant couples (91%, 95%CI: 79-96%) [30].

Third, we assessed the protective effect of early ART by computing the number of infections averted yearly for 10,000 persons after one year of treatment, which we estimated between 113 and 212. Those results rely on strong assumptions regarding the frequency of sexual intercourses and the stability over time of the ART preventive effect in the first year of treatment. Despite the uncertainty surrounding these assumptions, our results are quite consistent with previous studies. The sensitivity analysis we conducted on the sub-sample of stable serodiscordant couples allowed us to estimate HIV-incidence rateswhich were in the same range than those reported by the HPTN052 study [3]. Moreover, a previous model estimated that providing early (350<CD4<500) ART to serodiscordant couples might be expected to avert 210 infections per 10,000 person-years on ART [31]. Our estimate of 161/10,000 is lower, which is consistent with the fact that our study included a broader population than serodiscordant couples, among which a substantial part (those sexually inactive and/or engaged in seroconcordant partnerships) do not benefit from the preventive effect of ART.

Our results were obtained in a population with early HIV diagnosis engaged in a 30-monthtrial. The sex ratio was unbalanced in favor of women, which reflects both the sex-specific prevalence of HIV (6.4% and 2.9%, respectively [20]) and delayed diagnosis among men, who have lower opportunities of early diagnoses than women in Côte d'Ivoire [32].Even if participants of the present

study potentially constitute a compliant population engaged in a trial offering good care conditions, the proportion of viral suppression achievement in participants on early ART 12 months after enrollment (83%) was not dramatically higher than that documented in population-based studies throughout sub-Saharan Africa [33]. This suggests that our results are likely to be in the range of figures observed more widely in West-Africa.

Our study has some limitations.

First, the present behavioral study was nested in a randomized controlled 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 [15], our results were obtained in the absence of specific information message about the preventive effect of ART. The current study may therefore only partially address the issue of risk compensation. Further research questioning risk perception in the context of widely available information about preventive effect of early ART is needed, both among HIV-infected and uninfected people.

Second, the results of this study largely rely on self-reported sexual behaviors, which are potentially subject to social desirability bias. Over-report of condom use could lead to an underestimation of the estimated HIV transmission risks. However, since counseling and follow-up were similar between both ART groups, such a bias is unlikely to be differential and thus to have affectedour estimate of the preventive effect of early ART.

Third, estimates of HIV transmission risk were based on the characteristics of the last sexual intercourse. This might have biased the analysis if the frequency of sexual intercourses differed between both groups, and/or if there were differencesbetween groups in the extent to which the last sexual intercourse reflected overall sexual behaviors. Such differences are unlikely, though, given that both groups were comparable forvarious indicators, including sexual activity and multiple partnerships.

Fourth, differences between ART strategies in the proportionof non-response to the M12 questionnaire might have biased estimations of HIV-transmission risk. Alowerproportion of participants on standard *vs.* early ART completed the questionnaire during the considered window period, *i.e.* between M9 and M15. Patients who completed the questionnaire out of this periodwere mostly individuals randomized to standard ART, who initiated ART during the first 12 months of follow-up, which rescheduled subsequent visits and questionnaire completions from the date of ART initiation. Compared to other patients on standard ART, patients who started treatment before the 12-month

visitprobably had higher VL, and therefore higher infectiousness, in their pre-ART period; and then lower VL and infectiousness in their ART-period. When considering the whole M0-M12 period, excluding these patients may have led to limited bias in the estimates of the transmission risk among those on standard ART and of the protective effect of early ART.In addition, missing 12-month visit during the window periodwere more frequent among patients on early ART(38 *vs.* 17). In 2011, because of the political crisis faced by Côte d'Ivoire, the Temprano staff anticipated violence in Abidjan and predictable disruption of health services by giving in advance a higher stock of drugs to patients [34]. Thus, treated patients might have delayed their 12-month visit without being necessarily out of treatment.

Expanding ART coverage has resulted in decreased HIV incidence in South Africa [35], but other "natural experiments" showed limited effecton HIV transmission, especially when risk compensation was observed [36]. Community trials have started to formally assess the effect of early ART on HIV incidence, but their results will not be released before several years. Meanwhile, our results suggest a strong protective effect of early ART on HIV heterosexual transmission without any detectable effecton sexual behaviors. This effect was estimated in a population including substantial proportions of persons out of stable partnership or with a seroconcordant partner, thus closer to the whole HIV-infected population than previous studies restricted to stable serodiscordant couples. WHO has recently recommended early ART initiation for people living in serodiscordant couple [15]. The social acceptability and equity of prioritizing access to early ART to this population is questionable though[37]. Recent modeling studies on the contribution of HIV-transmissions occurring among stable serodicordant couples to the global sub-Saharan HIV epidemics demonstrated that prevention interventions targeted solely on those couples may have a limited public health impact [16,38]. Our results provide evidence for the public health significance of early ART initiation among a wider segment of the HIV-infected population.

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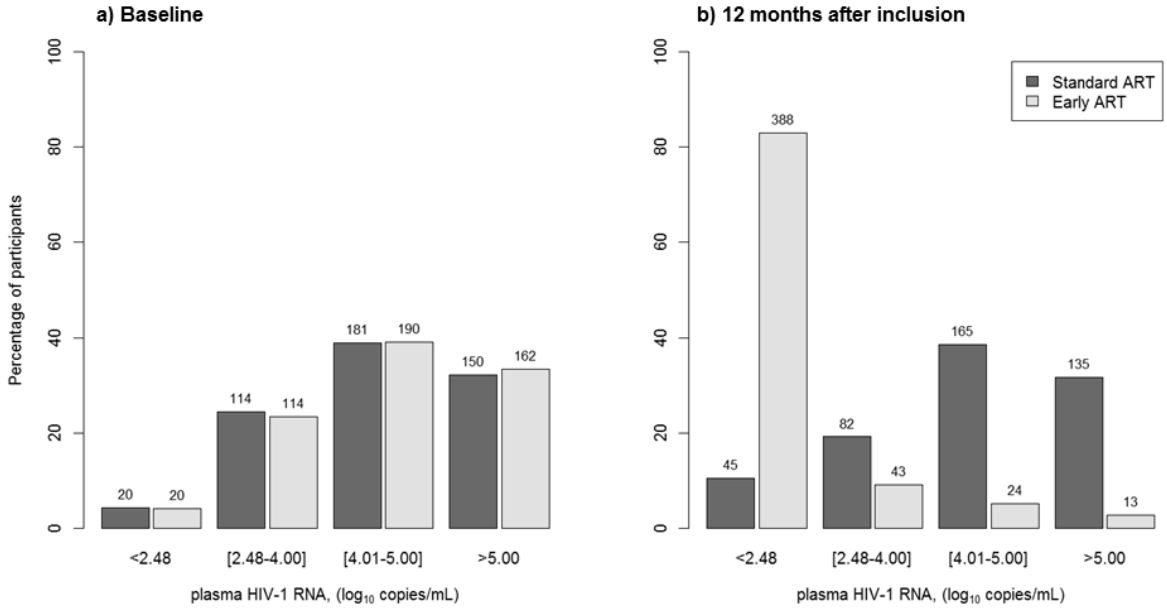
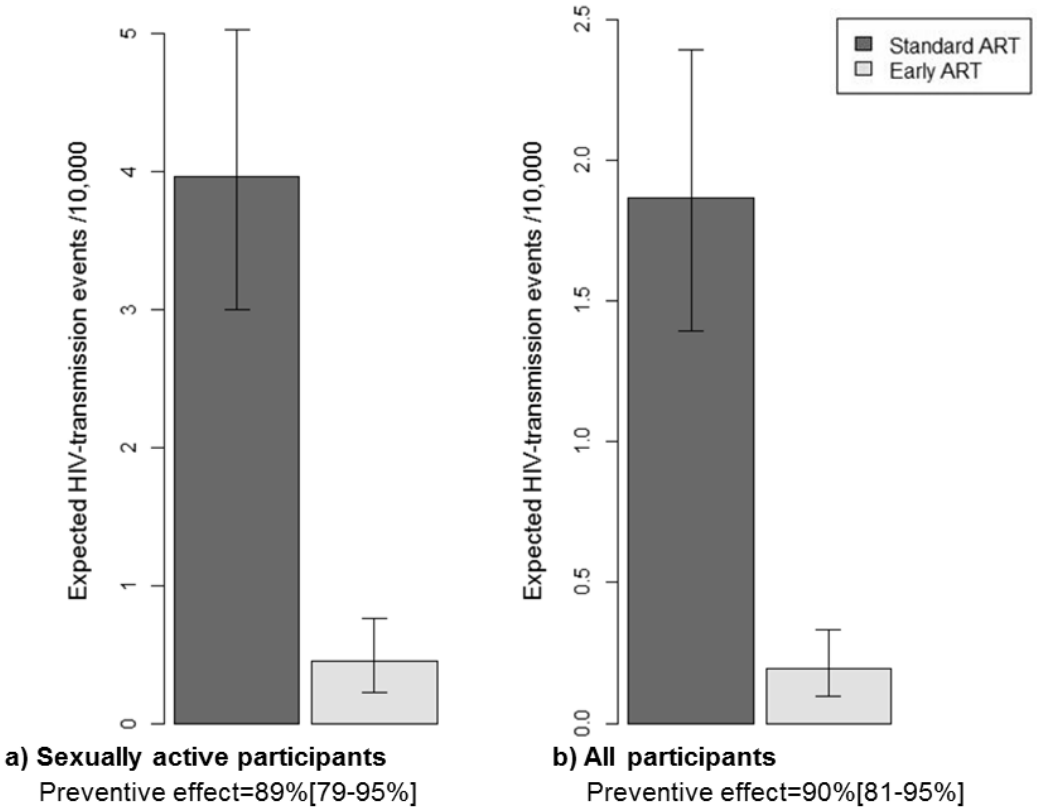
FIGURES& TABLES

Figure 1:Distribution of plasma HIV-1 RNA, in log_{10}copies/ml by ART strategy. Expressed as Log_{10} (VL);**a) At baseline.** Standard ART: undetectable VL: 4.3%; detectable VL: mean(log_{10} copies/ml) [95%IC] =4.60 [4.52-4.68]. Early ART: undetectable VL: 4.1% detectable VL: mean(log_{10} copies/ml) [95%IC] = 4.63 [4.55-4.71]. **b) 12 months after inclusion.** Standard ART: undetectable VL: 12.5%; detectable VL: mean(log_{10} copies/ml) [95%IC] = 4.68 [4.60-4.76]. Early ART: undetectable VL: 82.9% detectable VL: mean(log_{10} copies/ml) [95%IC] = 3.88 [3.66-4.11].



Footnotes: log_{10} (HIV-1 RNA) <2.48 corresponds to the detectability threshold of HIV-1 RNA<300 copies/mL

Figure 2:EstimatedHIV-transmission rates at last sexual intercourse in the last month, by ART strategy. Socio-behavioral study nested in the Temprano trial, M12 visit (N=957). **a)** for 10,000 sexually active participants, **b)** for 10,000 participants.



Footnotes: Per-act VL-specific transmission probabilities are derived from Hughes *et al.*, 2012 [19]. Calculation accounted for sexual activity, condom use, circumcision and partner's HIV status.

Table 1:Baseline characteristics, by ART strategy. Socio-behavioral study nested in the Temprano trial (N=957).

		Standard ART N=467 n (%)	**Early ART N=490** n (%)	**p**
Sex				0.78
	Men	93 (19.91%)	94 (19.18%)	
	Women	374 (80.09%)	396 (80.82%)	
Age (years)				0.30
	<30	118 (25.27%)	118 (24.08%)	
	30-40	217 (46.47%)	211 (43.06%)	
	>40	132 (28.27%)	161 (32.86%)	
Educational level				0.10
	None	94 (20.13%)	131 (26.73%)	
	Primary	144 (30.84%)	137 (27.96%)	
	Secondary	170 (36.40%)	170 (34.69%)	
	>Secondary	59 (12.63%)	52 (10.61%)	
Personal source of income				0.44
	No	116 (26.07%)	134 (28.33%)	
	Yes	329 (73.93%)	339 (71.67%)	
Family status				0.52
	Single	200 (42.83%)	203 (41.43%)	
	Living in union	218 (46.68%)	224 (45.71%)	
	Separated/widowed	49 (10.49%)	63 (12.86%)	
Perceived health				0.12
	Excellent/Very good	100 (21.69%)	99 (20.45%)	
	Good	298 (64.64%)	295 (60.95%)	
	Poor/Bad	63 (13.67%)	90 (18.60%)	
WHO clinical stage				0.97
	1	290 (62.10%)	310 (63.27%)	
	2	125 (26.77%)	124 (25.31%)	
	3	50 (10.71%)	54 (11.02%)	
	4	2 (0.43%)	2 (0.41%)	
CD4 cell count /mm^3				0.44
	<350	71 (15.2%)	88 (17.9%)	
	350-499	176 (37.7%)	187 (38.2%)	
	≥500	220 (47.1%)	215 (43.9%)	

Table 2: Sexual behaviors in the past 12 months, by ART group. Socio-behavioral study nested in the Temprano trial, M12 visit (N=957).

	Standard ART n (%)	**Early ART** n(%)	**p**
Overall	*N=467*	*N=490*	
Sexually activein the past year	335 (71.7)	342 (69.8)	0.51
Multiple partnership	29 (6.2)	44 (9.0)	0.11
Among those sexually activein the past year	*N=335*	*N=342*	
Last intercourse with a cohabiting partner			
Yes	197 (58.8)	199 (58.2)	0.87
No	138 (41.2)	143 (41.8)	
Last partner's HIV status			
HIV-negative	89 (26.6)	78 (22.8)	0.47
HIV-positive	99 (29.6)	101 (29.5)	
Unknown	147 (43.9)	163 (47.7)	

Table 3: Characteristics of the last intercourse in the past month, by ART group. Socio-behavioral study nested in the Temprano trial, M12 visit (N=957).

	Standard ART (N=467) n (%)	**Early ART (N=490)** n (%)	**p**
Last intercourse in the past month	226 (48.4)	214 (43.7)	0.14
Unprotected sex at last intercourse*	100 (21.4)	76 (15.5)	0.06
Risky sex [1] at last intercourse*	60 (12.9)	49 (10.0)	0.54
Partner's exposure to HIV [2] at last intercourse*	50 (10.7)	12 (2.45)	$<10^{-3}$

* Last intercourse in the past month

[1] Unprotected sex with a partner of HIV-negative/unknown status

[2] Unprotected sex with a partner of HIV-negative/unknown status, and HIV viral load>300 copies/mL

Table 4: Sensitivity analyses of estimated HIV-transmission rates at last intercourse in the past month (per 10,000 persons) and estimated protective effect of early ART strategy. Socio-behavioral study nested in the Temprano trial, M12 visit (N=957).

Population	Number of participants	Reference for VL-specific HIV transmission probabilities	Specific assumption	Expected HIV-transmissions at lastsexual intercourse in the past month, for 10,000 persons [95%CI]		Protective effect [95%CI]
				Standard arm	Early arm	
Total sample	Standard arm; n=467; Early arm: n=490	Hughes *et al.* [19]	**Main analysis**	1.87 [1.39-2.39]	0.20 [0.09-0.33]	**90% [81-95%]**
Baseline CD4 count>350	Standard arm; n=396; Early arm: n=402	Hughes *et al.* [19]	Same as in the main analysis	2.03 [1.47-2.66]	0.20 [0.08-0.36]	**90% [81-96%]**
Cohabiting serodiscordant couples	Standard arm; n=55; Early arm: n=54	Hughes *et al.* [19]	Same as in the main analysis	3.36 [2.11-4.78]	0.37 [0.14-0.64]	**89% [77-96%]**
Total sample	Standard arm; n=467; Early arm: n=490	Hughes *et al.* [19]	VL=300 copies/mLfor patients with undetectable VL	1.88 [1.40-2.40]	0.30 [0.19-0.43]	**84% [75-90%]**
Total sample	Standard arm; n=467; Early arm: n=490	Gray *et al.* [22]	Same as in the main analysis	1.72 [1.36-2.11]	0.25 [0.14-0.4]	**85% [75-92%]**
Total sample	Standard arm; n=467; Early arm: n=490	Hughes *et al.* [19]	40% of partners with unknown HIV status considered as HIV-positive	1.34 [1.01-1.70]	0.13 [0.07-0.22]	**90% [82-95%]**
Total sample	Standard arm; n=467; Early arm: n=490	Hughes *et al.* [19]	All participants considered as having hada last unprotected intercourse with a HIV-negative partner	18.4 [16.6-20.3]	2.1 [1.4-2.9]	**89% [84-92%]**