What Level of Risk Compensation Would Offset the Preventive Effect of Early Antiretroviral Therapy? Simulations From the TEMPRANO Trial

Kévin Jean, Marie-Claude Boily, Christine Danel, Raoul Moh, Anani Badjé,
Annabel Desgrées-Du-Loû, Serge Eholié, France Lert, Rosemary Dray-Spira,
Xavier Anglaret, et al.

(Brief Original Contribution)

What Level Of Risk Compensation Would Offset the Preventive Effect of Early ART?

Simulations from the TEMPRANO Trial (Abidjan, Côte d'Ivoire)

Kévin Jean, Marie-Claude Boily, Christine Danel, Raoul Moh, Anani Badgé, Annabel Desgrées-du-Loû, Serge Eholié, France Lert, Rosemary Dray-Spira, Xavier Anglaret, Eric Ouattara.

Footnotes page

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; VL, viral load; WHO, World Health Organization.

Correspondence: Kévin Jean, Imperial College London, Dept. of Infectious Diseases Epidemiology, St Mary's Campus, Norfolk Place, London, W2 1PG, United Kingdom (kevin.jean.lab@gmail.com).

Running head: Early ART and risk compensation

ABSTRACT

Whether or not risk compensation could offset the preventive effect of early antiretroviral therapy (ART) on heterosexual HIV transmission remains unknown. Using virological and behavioral data collected 12 months after inclusion in the TEMPRANO-ANRS12136 randomized controlled trial of early ART (Abidjan, Côte d'Ivoire), we estimated the risk of HIV transmission and compared it between the intervention (early ART, n=490) and control (deferred ART, n=467) groups. We then simulated increases in various sexual risk behaviors in the intervention group and estimated the resulting preventive effect. Based on reported values of sexual behaviors, we estimated an 89% (95% Confidence Interval: 81%, 95%) preventive effect of early ART on the cumulative HIV transmission risk over a one-month period. This preventive effect remained significant for a wide range of parameters combinations and was offset (ie non-significant) only for dramatic increases simulated simultaneously in different sexual behaviors. For example, when considering a two-fold increase in serodiscordance and the frequency of sexual intercourse together with a 33% decrease in condom use, the resulting preventive effect was 47% (95%CI: -3%, 74%). An important reduction of HIV transmission in the short-term may thus be expected from the scale-up of early ART, even in the context of behavioral change.

(Abstract word count: 200 words)

(Main text word count: 1967 words)

Early antiretroviral therapy (ART) is a promising strategy to curb the HIV/AIDS epidemic, especially in sub-Saharan Africa. Through its effect on HIV replication, early ART reduces the risk of HIV transmission to uninfected sexual partners (1). However, it remains unclear as to whether risk compensation—an increase in sexual risk behaviors resulting from a decrease in the perceived risk of transmission—could result from expanded use of ART and whether or not it could offset its preventive effect.

Changes in risk behaviors have been suggested to explain limited decreases in HIV incidence associated with ART expansion in various settings (2,3). However, numerous studies including a meta-analysis have reported a decrease in sexual risk behaviors after ART initiation in patients with low CD4 count or advanced HIV disease (4–6). Few studies have assessed behavioral changes in healthier heterosexual individuals initiating ART earlier. A recent study nested in the TEMPRANO-ANRS12136 early ART randomized controlled trial has documented no effect of early ART initiation on sexual behaviors as compared to pre-2015 WHO-guided ART initiation (7). Nevertheless, generalizability of these results may be limited by the fact that they were obtained in a trial context in which the treatment was proposed to the participants for their own benefits, without any information on its potential preventive benefit.

In the absence of clear experimental evidence for risk compensation associated with early ART, we used computer simulations relying on individual data collected within the TEMPRANO-ANRS12136 trial with a previously developed methodology (8) to assess the levels of increase in sexual risk behaviors that would be needed to offset the preventive benefit of early ART 12 months after initiation.

METHODS

The TEMPRANO trial

TEMPRANO is a randomized controlled trial conducted between March 2008 and December 2014 in Abidjan (Côte d'Ivoire) to assess the individual benefits and risks of early ART initiation in adults (9). The main inclusion criteria were: i) CD4 < 800 / mm^3 and ii) no WHO criteria for ART initiation. After inclusion, consenting patients were randomized to initiate ART either immediately (early ART) or according to the current WHO guidelines (deferred ART). In addition to the clinical and biological monitoring data (CD4-count, viral load [VL]), the trial harbored a behavioral study, allowing a yearly collection of information about sexual behaviors, including sexual activity (ie at least one sexual intercourse) in the past month, reported HIV status of the most recent partner (positive/negative/unknown) and condom use at the most recent intercourse.

The present analysis includes 957 participants (early ART: 490; deferred ART: 467; median age: 35; 80.5% women) enrolled in the trial between 1 January 2009 and 1 September 2011, provided they completed a behavioral questionnaire within 9–15 months after enrolment.

At 12 months, 82.9% of the participants in the early ART group had achieved virological control (detectability threshold: 300 copies/mL) versus 10.5% in the deferred ART group (all of these participants with undetectable VL having initiated ART according to current guidelines; χ², *P*<0.0001). In the early ART group, 30.2% of the participants had their most recent sexual intercourse in the past month with a serodiscordant partner (deferred ART: 32.5 %; χ², *P* = 0.43) and 66.9 % reported having used a condom (deferred ART: 60.5 %; χ², *P* = 0.25) (8).

Base case: estimating the preventive effect of early ART

In both ART groups 12 months after inclusion in the trial, we estimated individual HIV transmission risk during the last month, r_{ij}, where i indexes individuals from ART group j (deferred ART: j = 1; early ART: j = 2). Individual r_{ij} values were calculated using Equation 1 (Figure 1), based on demographic variables (gender, age), VL and the following behavioral parameters: (i) a term combining sexual activity and reported partner's HIV status, S_{ij} (S_{ij} = 0 if not sexually active or if the most recent sex act was with a

concordant HIV-positive partner; $S_{ij} = 1$ otherwise); (ii) condom use (C_{ij}) and (iii) the monthly frequency of sexual intercourse (k_{ij}). The coefficients for r_{ij} estimation were derived from a multi-country seroconversion study (Supplementary Text 1) (10).

Partners with unknown HIV status were considered HIV uninfected. Transmission risk was set to zero in case of undetectable VL (ie <300 cp/μL) (11,12). The risk of transmission was estimated at last sexual intercourse ($k_{ij} = 1$) or cumulated over a one-month period, assuming a mean monthly number of eight sexual intercourses (13,14).

Individual risks of HIV transmission (r_{ij}) were averaged among participants from each ART group (Figure 1, Equations 2.1 and 2.2) to estimate the preventive effect of early ART (Figure 1, Equation 3).

Varying the effect of risk compensation associated with early ART

To explore the potential impact of risk compensation associated with early ART, we varied the levels of serodiscordant sexual activity and condom use among the early ART group only and estimated the resulting average risk that we compared to the observed average risk of the deferred ART group (Figure 1).

To vary the group-level expected value of serodiscordant sexual activity $\overline{S_{j=2}}$: i) we generated different Bernoulli distributions with probabilities between 10% and 100%; ii) for each distribution we randomly selected individual values S_{i2} and then estimated individual r_{i2} using Equation 1 (Figure 1); iii) we computed $\overline{r_{i2}}$ and estimated the preventive effect of early ART by dividing $\overline{r_{i2}}$ by the observed average risk $\overline{r_{i1}}$, obtained among the deferred ART group in the base case (ie with observed S_{i1} values) ; iv) we computed 95% confidence intervals for preventive effect estimates using bootstrap resampling (2,000 samples). We repeated the above steps while varying the expected value of condom use $\overline{C_{j=2}}$ instead of $\overline{S_{j=2}}$, and finally while varying both parameters simultaneously. We also considered an additional scenario where we simultaneously varied these parameters and stimulated a two-fold increase in the monthly frequency of sexual intercourse in the early ART group. Note that when considering the risk of transmission cumulatively over a one-month period, we extrapolated the condom use reported for the most recent intercourse to all intercourses assumed over this period.

Analyses were performed using R software v2.15.1.

RESULTS

Base case and univariate variations

Based on the reported values of condom use and serodiscordant activity in the early ART group (base case scenario) and considering the last sexual intercourse ($k_{j=1} = k_{j=2} = 1$), we previously estimated a reduction in the HIV transmission risk of 90% (81%, 95%) in the early ART group (8). This estimated preventive effect of the intervention varied from 98.7% (94.2%, 99.9%) to 82% (69%, 90%) when serodiscordant sexual activity increased from 10% to 100%, respectively (Figure 2.A.). Estimates varied from 94% (87%, 98%) to 73% (35%, 90%) when condom use decreased from 100% to 0%, respectively (Figure 2.B). Based on the reported values of S_{ij} and C_{ij}, the preventive effect of early ART did not change substantively when considering cumulative risks over the last month (89% [81%, 95%]) instead of a single intercourse.

Multivariate variations

Figure 2.C and 2.D show the variation of the preventive effect of early ART when varying simultaneously three parameters: the percentage of condom use, the percentage of serodiscordant activity and the monthly number of intercourses. When assuming the same average number of monthly intercourses in early and deferred groups ($\overline{k_{j=1}} = \overline{k_{j=2}} = 8$), the preventive effect of early ART was offset (ie non-significant) for group-level condom use ≤10% concomitantly with serodiscordant activity ≥90% (Figure 2.C). When doubling the average monthly frequency of sexual intercourse in the early group ($\overline{k_{j=1}} = 16$), compared to the deferred group ($\overline{k_{j=1}} = 8$), the preventive effect of the intervention was offset for a wider range of combinations between condom use and serodiscordant activity (Figure 2.D). For example, for 60% serodiscordance and 40% condom use, the preventive effect was 47% (-3%, 74%). In the worst-case scenario, the central value of early ART preventive effect was negative, though non-significantly (-30% [-119%, 24%]).

DISCUSSION

This study showed that a phenomenon of risk compensation - if it exists - should reach quite unrealistic levels to offset the short term preventive benefits of early ART compared with deferred ART initiation. Our model predicts that such an offset should occur only in the event of a simultaneous and substantial increase in several key sexual behaviors: a two-fold increase in the frequency of sexual intercourse and serodiscordance (60% versus 32.5% for deferred ART) and a 33% decrease in condom use (40% versus 60.5% for deferred ART).

By reducing the VL of the HIV-infected persons to an undetectable level, ART may theoretically prevent HIV transmissions (11,12,15). In the TEMPRANO trial, more than 4 out of every 5 treated patients in the early ART group achieved viral suppression 12 months after ART initiation. In that case, if behavioral change occurs, it may result in an increased risk of transmission only among the approximately 20% of participants who did not achieve viral suppression. This explains the magnitude of our estimated preventive effect of early ART even at high levels of risk compensation. This preventive effect is likely to remain high in the long term under conditions of high levels of retention in care and adherence to treatment.

Significant increases in sexual risk behaviors related to ART have been documented previously. However, such increases were mostly observed among individuals from high-risk groups who were initially deeply immunocompromised, for whom ART allowed health recovery and the possible return to sexual activity (16,17). Comparable increases in sexual risk behaviors in patients at an early stage of HIV infection are less likely. Moreover, more recent results suggest that early entry into HIV care, with or without ART initiation, may be followed by a decrease in sexual risk behaviors (7).

Our results were obtained from a population of patients recruited in nine different clinical centers where all eligible patients were systematically approached. The quite low refusal rate (16%) suggests a limited selection bias. The sex ratio favoring women may reflect the national context of higher HIV prevalence and higher opportunities for early diagnoses for women compared to men (18). The proportion of viral suppression achieved in participants receiving early ART 12 months after enrolment (83%) was not dramatically higher than that documented in population-based studies throughout sub-Saharan Africa

(19). Together, all the elements above are in favor of the generalizability of our findings outside the setting of a clinical trial.

Our study has several limitations. We explored the potential impact of risk compensation based on VL measured 12 months after early ART initiation. Risk compensation may have a higher mitigating impact on ART preventive effect if occurring in the first months following ART initiation, before VL suppression is achieved (20). We accounted for the last sexual partner only and estimated the risk of HIV transmission over a number of sexual intercourses corresponding to a relatively short time period. Nevertheless, extrapolating over a longer time period or to several sexual partners may have led to potentially unreliable results. Our estimates assume that risk compensation occurs similarly among adherent and non-adherent patients. However, patients being prescribed ART without actually using it could be less likely to perceive a reduced risk of HIV transmission and, consequently, to engage in risk compensation. This may have led to an overestimation of the detrimental effect of risk compensation on early ART preventive benefits.

The concern of risk compensation has been raised for almost every innovation in HIV prevention (21). However, results have shown that this phenomenon can be prevented by offering interventions in combination with traditional prevention methods (such as counselling or condom promotion) (22,23). Our results suggest that even if risk compensation occurred among HIV-positive patients on early ART, it would unlikely be able to counter-balance its preventive benefit. A dramatic reduction of HIV transmission might be actually expected from the scaling up of early ART even in the context of behavioral change. However, the promotion of sexual health remains a priority to alleviate the burden of sexually transmitted diseases and other sex-related risks.

REFERENCES

1. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N. Engl. J. Med.* 2011;365(6):493–505.

2. Wilson DP. HIV Treatment as Prevention: Natural Experiments Highlight Limits of Antiretroviral Treatment as HIV Prevention. *PLoS Med.* 2012;9(7):e1001231.

3. Eaton JW, Bacaër N, Bershteyn A, et al. Assessment of epidemic projections using recent HIV survey data in South Africa: a validation analysis of ten mathematical models of HIV epidemiology in the antiretroviral therapy era. *Lancet Glob. Health.* 2015;3(10):e598–e608.

4. Kennedy C, O'Reilly K, Medley A, et al. The impact of HIV treatment on risk behaviour in developing countries: a systematic review. *AIDS Care.* 2007;19(6):707–720.

5. Berhan A, Berhan Y. Is the Sexual Behaviour of HIV Patients on Antiretroviral therapy safe or risky in Sub-Saharan Africa? Meta-Analysis and Meta-Regression. *AIDS Res. Ther.* 2012;9(1):14.

6. Kaye DK, Kakaire O, Osinde MO, et al. The impact of highly active antiretroviral therapy on high-risk behaviour of HIV-infected patients in sub-Saharan Africa. *J. Infect. Dev. Ctries.* 2013;7(6):436–447.

7. Jean K, Gabillard D, Moh R, et al. Decrease in sexual risk behaviours after early initiation of antiretroviral therapy: a 24-month prospective study in Côte d'Ivoire. *J. Int. AIDS Soc.* 2014;17:18977.

8.   Jean K, Gabillard D, Moh R, et al. Effect of early antiretroviral therapy on sexual behaviors and HIV-1 transmission risk among adults with diverse heterosexual partnership statuses in Côte d'Ivoire. *J. Infect. Dis.* 2014;209(3):431–440.

9.   TEMPRANO ANRS 12136 Study Group, Danel C, Moh R, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *N. Engl. J. Med.* 2015;373(9):808–822.

10.   Hughes JP, Baeten JM, Lingappa JR, et al. Determinants of per-coital-act HIV-1 infectivity among African HIV-1-serodiscordant couples. *J. Infect. Dis.* 2012;205(3):358–365.

11.   Attia S, Egger M, Müller M, et al. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. *AIDS Lond. Engl.* 2009;23(11):1397–1404.

12.   Loutfy MR, Wu W, Letchumanan M, et al. Systematic review of HIV transmission between heterosexual serodiscordant couples where the HIV-positive partner is fully suppressed on antiretroviral therapy. *PloS One.* 2013;8(2):e55747.

13.   Blower SM, Boe C. Sex acts, sex partners, and sex budgets: implications for risk factor analysis and estimation of HIV transmission probabilities. *J. Acquir. Immune Defic. Syndr.* 1993;6(12):1347–1352.

14.   Allen S, Meinzen-Derr J, Kautzman M, et al. Sexual behavior of HIV discordant couples after HIV counseling and testing. *AIDS Lond. Engl.* 2003;17(5):733–740.

15.   Rodger A, Bruun T, Cambiano V, et al. HIV Transmission Risk Through Condomless Sex If HIV+ Partner On Suppressive ART: PARTNER Study. 2014;

16.   Dukers NH, Goudsmit J, de Wit JB, et al. Sexual risk behaviour relates to the virological and immunological improvements during highly active antiretroviral therapy in HIV-1 infection. *AIDS Lond. Engl.* 2001;15(3):369–378.

17.   Tun W, Gange SJ, Vlahov D, et al. Increase in sexual risk behavior associated with immunologic response to highly active antiretroviral therapy among HIV-infected injection drug users. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* 2004;38(8):1167–1174.

18.   Jean K, Anglaret X, Moh R, et al. Barriers to HIV Testing in Côte d'Ivoire: The Role of Individual Characteristics and Testing Modalities. *PLoS ONE.* 2012;7(7):e41353.

19.   Barth RE, van der Loeff MFS, Schuurman R, et al. Virological follow-up of adult patients in antiretroviral treatment programmes in sub-Saharan Africa: a systematic review. *Lancet Infect. Dis.* 2010;10(3):155–166.

20.   Mujugira A, Thomas K, Celum C, et al. HIV-1 Transmission Risk Persists During the First 6 Months of Antiretroviral Therapy. 2015;(http://www.croiconference.org/sessions/hiv-1-transmission-risk-persists-during-first-6-months-antiretroviral-therapy). (Accessed October 8, 2015)

21.   Cassell MM, Halperin DT, Shelton JD, et al. Risk compensation: the Achilles' heel of innovations in HIV prevention? *BMJ.* 2006;332(7541):605–607.

22.   Kong X, Kigozi G, Nalugoda F, et al. Assessment of changes in risk behaviors during 3 years of posttrial follow-up of male circumcision trial participants uncircumcised at trial closure in Rakai, Uganda. *Am. J. Epidemiol.* 2012;176(10):875–885.

23.   Fisher JD, Cornman DH, Shuper PA, et al. HIV Prevention Counseling Intervention Delivered During Routine Clinical Care Reduces HIV Risk Behavior in HIV-Infected South Africans Receiving Antiretroviral Therapy: The Izindlela Zokuphila/Options for Health Randomized Trial. *J. Acquir. Immune Defic. Syndr. 1999.* 2014;

SUPPLEMENTARY MATERIAL

Supplementary Text 1: Equation of Per-coital HIV-1 Transmission Risk and Sensitivity to Parameters Coefficients.

FIGURES

$$r_{ij} = 1 - \left(1 - S_{ij}(1 - 0.78\,C_{ij})(1 - 0.53\,W_{ij})\left(1 - e^{-e^{\left(-7.257 + 1.070\left(Log(VL_{ij}) - 4\right) - 0.025\left(age_{ij} - 35\right)\right)}}\right)\right)^{k_{ij}} \quad (1)$$

Deferred ART (j=1)

$r_{i1}(S_{i1}, C_{i1}, W_{i1}, VL_{i1}, age_{i1}, k_{i2})$ (1.1)

$W_{i1}, VL_{i1}, age_{i1}$ observed;

Base case : S_{i1}, C_{i1} observed (reported),
$k_{i1} = 1$;

Simulations: S_{i1}, C_{i1} observed (reported), k_{i1} selected from a Poisson distribution with parameter $\lambda=8$;

$$\bar{r}_{i1} = \frac{\sum r_{i1}}{n_{j=1}} \quad (2.1)$$

Early ART (j=2)

$r_{i2}(S_{i2}, C_{i2}, W_{i2}, VL_{i2}, age_{i2} k_{i2})$ (1.2)

$W_{i2}, VL_{i2}, age_{i2}$ observed;

Base case : S_{i2}, C_{i2} observed (reported),
$k_{i2} = 1$;

Simulations: S_{i2}, C_{i2} selected from Bernoulli distributions with probabilities between 0 and 100% corresponding to $\overline{S_{i2}}$ or $\overline{C_{i2}}$, variations respectively, k_{i2} selected from a Poisson distribution with parameter $\lambda=8$ or $\lambda=16$;

$$\bar{r}_{i2} = \frac{\sum r_{i2}}{n_{j=2}} \quad (2.2)$$

$$\textbf{\textit{Preventive effect}} = 100 \left(1 - \frac{\bar{r}_{i1}}{\bar{r}_{i2}}\right) \quad (3)$$
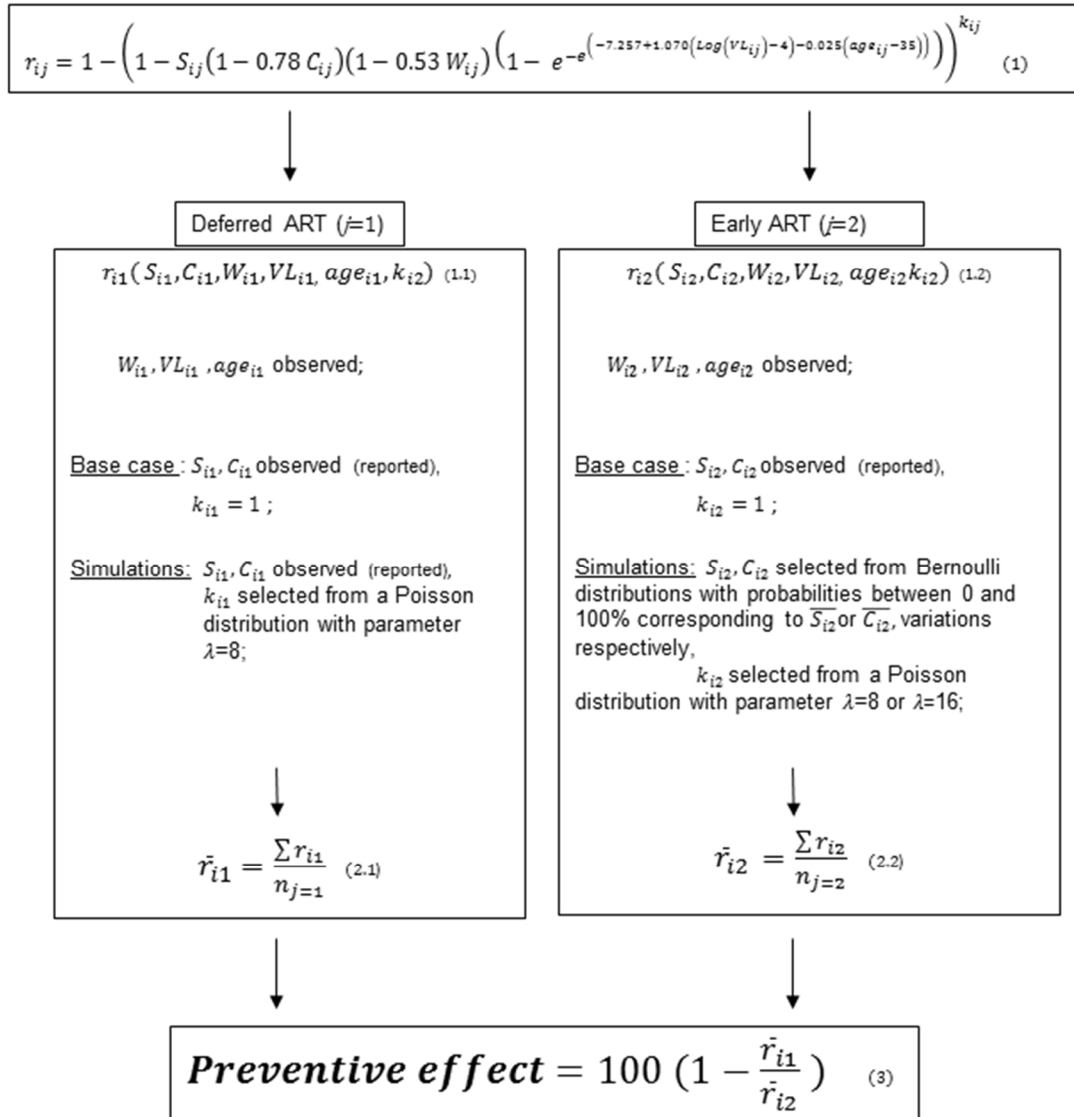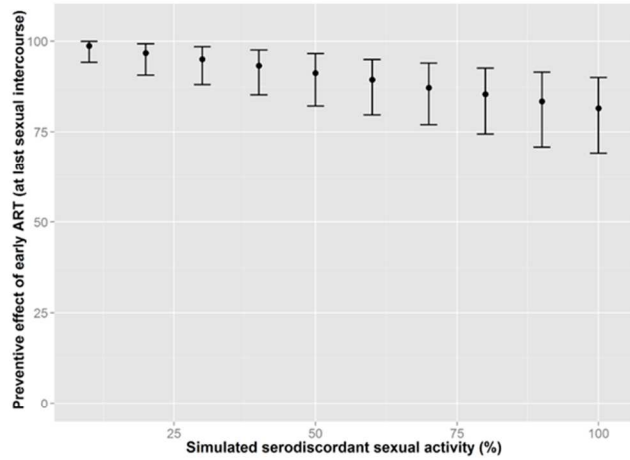
Figure 1. Schematic representation of the method and equations used to estimate individual risks of HIV transmission and the preventive effect of early ART on HIV transmission risk compared with deferred ART initiation.
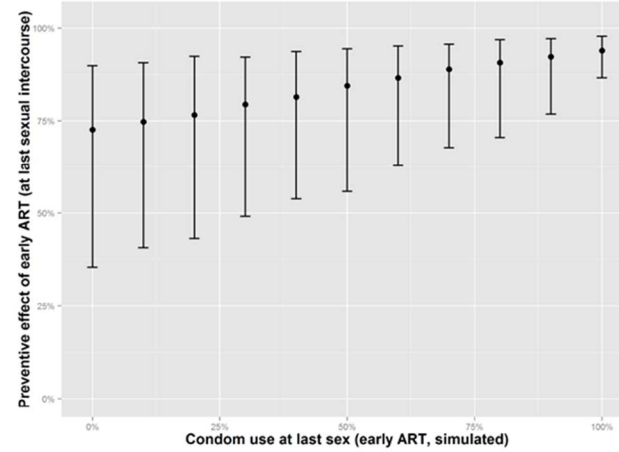
r_{ij} : cumulative risk of HIV transmission over k_{ij} sexual intercourse from the index individual i from ART group j (deferred ART: j = 1; early ART: j = 2) to its most recent partner; S_{ij} : serodiscordant sexual activity (S_{ij} = 0 if not sexually active or if the most recent sex act was with a concordant HIV-positive partner; S_{ij} = 1 otherwise). C_{ij} : condom use (C_{ij} = 1 if the last intercourse was protected; C_{ij} = 0 otherwise). W_{ij} represents the gender of the index HIV-infected partner (W_{ij} = 1 if women, W_{ij} = 0 if men). This term thus accounts for the protection conferred by male circumcision, considering all

partnerships as heterosexual, and each last male sexual partner as being circumcised, which is a reasonable assumption in Côte d'Ivoire.
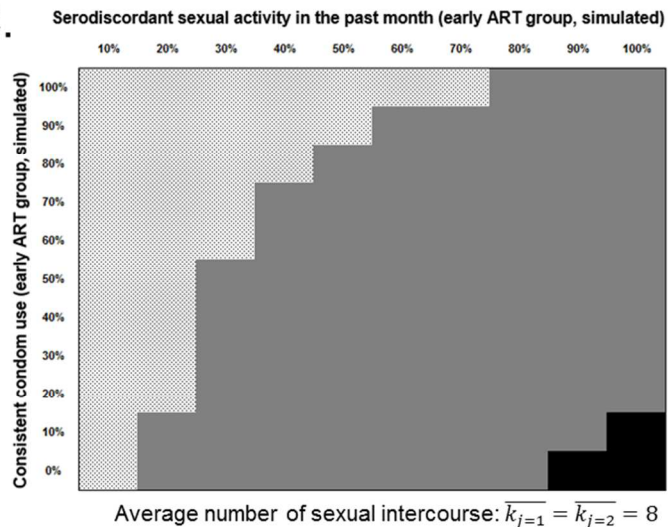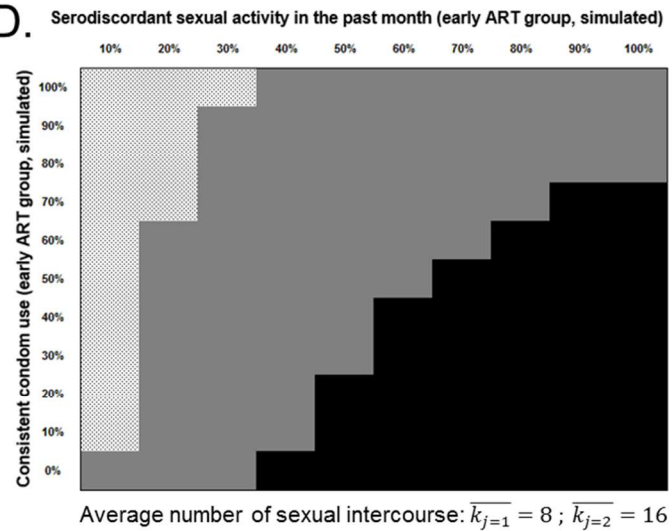
A.

Preventive effect of early ART (at last sexual intercourse)

Simulated serodiscordant sexual activity (%)

B.

Preventive effect of early ART (at last sexual intercourse)

Condom use at last sex (early ART, simulated)

C.

Serodiscordant sexual activity in the past month (early ART group, simulated)

10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

Consistent condom use (early ART group, simulated)

Average number of sexual intercourse: $\overline{k_{j=1}} = \overline{k_{j=2}} = 8$

D.

Serodiscordant sexual activity in the past month (early ART group, simulated)

10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

Consistent condom use (early ART group, simulated)

Average number of sexual intercourse: $\overline{k_{j=1}} = 8$; $\overline{k_{j=2}} = 16$

Significant preventive effect of early ART ($\geq$ 90%)　　Significant preventive effect of early ART (90% to 45%)　　Non significant preventive effect of early ART

Figure 2: Variations in the estimated preventive effect of early ART in response to changes in different sexual behaviours.

(A) and (B): Univariate analysis considering the last sexual intercourse and varying the group-level serodiscordant sexual activity (A) and condom use (B) in the early ART group.

(C) and (D) : Multivariate analysis varying simultaneously the group-level serodiscordant sexual activity and condom use and considering a cumulated HIV-transmission risk over a one-month period, with a monthly frequency of sexual intercourse in the early ART group equal (C) or doubled (D) as compared to the deferred ART group.

Results rely on comparison with 467 patients from the standard ART group. Among them 152 (32.5%) reported serodiscordant sexual activity, including 92 (60.5%) reporting condom use.