Imperial College
London

BSc Global Health 2011-2012
Module 1: In-Course Assessment 2

Date	11 November 2011
Time	90 minutes
Instructions	Please read the following extract of a scientific paper carefully and answer the questions using one or more answer booklet(s). Please answer each question on a new page of the booklet.

Title

Prevention of HIV-1 Infection with Early Antiretroviral Therapy (Cohen et al , 2011).

Background

Combination antiretroviral therapy decreases the replication of human immunodeficiency virus type 1 (HIV-1) and improves the survival of infected persons. Such therapy has been shown to reduce the amount of HIV-1 in genital secretions. Because the sexual transmission of HIV-1 from infected persons to their partners is strongly correlated with concentrations of HIV-1 in blood and in the genital tract, it has been hypothesized that antiretroviral therapy could reduce sexual transmission of the virus. Several observational studies have reported decreased acquisition of HIV-1 by sexual partners of patients receiving antiretroviral therapy. These results have been extrapolated to suggest that the use of early antiretroviral therapy could reduce the spread of the virus in a population. Some ecologic studies have shown a reduction in the incidence of new cases of HIV-1 after expanded use of antiretroviral therapy.

The effect of the timing of the initiation of antiretroviral therapy on clinical and microbiologic outcomes has been controversial in evaluations of the benefit of therapy and of the associated short- and long-term complications and costs. For many years, antiretroviral therapy was delayed until a patient's CD4 count fell below 200 cells per cubic millimeter, which led to frequent opportunistic infections. Retrospective analyses of patients with HIV-1 infection who were treated

in developed countries have suggested a benefit from early antiretroviral therapy, although the ability to control for bias in these studies has limits.

To evaluate the effect of combination antiretroviral therapy on the prevention of HIV-1 transmission to uninfected partners and on clinical events in infected persons, the HIV Prevention Trials Network (HPTN) conducted a multicontinent, randomized, controlled trial, called HPTN 052, to compare early versus delayed antiretroviral therapy for patients with HIV-1 infection who had CD4 counts between 350 and 550 cells per cubic millimeter and who were in a stable sexual relationship with a partner who was not infected.

Methods

Study Population

We enrolled HIV-1 serodiscordant couples at 13 sites in 9 countries (Gaborone, Botswana; Kisumu, Kenya; Lilongwe and Blantyre, Malawi; Johannesburg and Soweto, South Africa; Harare, Zimbabwe; Rio de Janeiro and Porto Alegre, Brazil; Pune and Chennai, India; Chiang Mai, Thailand; and Boston). A pilot phase started in April 2005, and enrollment took place from June 2007 through May 2010. Couples were required to have had a stable relationship for at least 3 months, to have reported three or more episodes of vaginal or anal intercourse during this time, and to be willing to disclose their HIV-1 status to their partner. Patients with HIV-1 infection were eligible if their CD4 count was between 350 and 550 cells per cubic millimeter and they had received no previous antiretroviral therapy except for short-term prevention of mother-to-child transmission of HIV-1. The study protocol was approved by at least one local institutional review board affiliated with each site, by boards affiliated with collaborating organizations, and by other local regulatory bodies when appropriate . All study participants provided written informed consent in their local languages, or English, if preferred.

Study Oversight

The study was funded by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health, which assumed all sponsor responsibilities through an investigational new drug application with the Food and Drug Administration (FDA). The antiviral agents that were used in the study were donated by pharmaceutical companies, which were not involved in the design or management of the study. All authors vouch for the completeness and accuracy of the data presented, as well as the fidelity of the report to the study protocol.

Study Design

HIV-1 serodiscordant couples were randomly assigned in a 1:1 ratio to either an early or delayed strategy for receipt of antiretroviral therapy. Permuted-block randomization was used with stratification according to site. In the early-therapy group, antiretroviral therapy was initiated in the partner with HIV-1 infection at enrollment. In the delayed-therapy group, therapy was initiated after two consecutive measurements in which the CD4 count was 250 cells per cubic millimeter or less or after the development of an illness related to the acquired immunodeficiency syndrome

(AIDS). HIV-1–infected participants who had active tuberculosis were excluded, and isoniazid prophylaxis was available, according to local guidelines and practice standards.

After enrolment, study participants were asked to attend three monthly visits, which were followed by quarterly visits unless they became ill or needed additional antiretroviral medications. HIV-1–infected participants who were receiving antiretroviral therapy had one additional visit 2 weeks after starting therapy. HIV-1–uninfected partners were encouraged to return for all visits together for counselling on risk reduction and the use of condoms, for treatment of sexually transmitted infections, and for management of other medical conditions. Some HIV-1–infected participants received trimethoprim–sulfamethoxazole prophylaxis, according to local guidelines.

HIV-1–uninfected partners were tested for HIV-1 seroconversion on a quarterly basis. Samples from all seroconversion events were evaluated at a central laboratory, and results were reviewed by an independent HIV end-point committee. Partners with seroconversion were released from the study and referred to a prearranged local clinic for care.

After the initiation of antiretroviral therapy, virologic failure for HIV-1–infected participants was defined as two consecutive plasma HIV-1 RNA measurements of more than 1000 copies per milliliter at 16 weeks or later. Assessment for clinical signs and symptoms, laboratory measurements, interviews about sexual behavior, review of adherence to the antiretroviral regimen (including a self-reported questionnaire and pill counts), and adherence counselling were conducted at each visit.

Any woman who was pregnant at enrollment or became pregnant was provided antiretroviral therapy appropriate for use during pregnancy at the start of the second trimester. On the basis of the judgment of the site investigator, women in the delayed-therapy group discontinued antiretroviral therapy after delivery or when breast-feeding ended. A new partner could be enrolled with an HIV-1–infected participant if the original partner was released from the study and the new HIV-1–uninfected partner met all inclusion or exclusion criteria.

Antiretroviral Drugs

Study drugs included a combination of lamivudine and zidovudine (Combivir), efavirenz, atazanavir, nevirapine, tenofovir, lamivudine, zidovudine, didanosine, stavudine, a combination of lopinavir and ritonavir (Kaletra and Aluvia), ritonavir, and a combination of emtricitabine and tenofovir (Truvada). A prespecified combination of these drugs was provided to participants at monthly or quarterly visits. Sites could also use locally supplied, FDA-approved drugs if they could be purchased with nonstudy funds. For participants with virologic failure, specified second-line treatment regimens were provided.

Assessment of Linkage of Seroconversions

To assess whether seroconversions were linked, HIV-1 *pol* gene sequences were generated by population sequencing for study-partner pairs and for 10 additional HIV-infected local control subjects for each relevant site. Sequences were analyzed with the use of phylogenetic methods. The probability of linkage was also assessed with the use of Bayes' theorem to compare the genetic similarity of HIV-1 from partner pairs with the genetic similarity of HIV-1 from local control subjects.

In some cases, HIV-1 samples from partner pairs were analyzed with the use of ultra-deep pyrosequencing of the gp41 region.

Statistical Analysis

We determined that an enrollment of 1750 serodiscordant couples would provide a power of at least 87% to detect a 39% reduction in the incidence of HIV-1 transmission to uninfected partners in the early-therapy group, as compared with the delayed-therapy group (primary prevention end point). By the end of the trial, we anticipated a total of 188 transmission incidences, with cumulative incidence rates of 8.3% in the early-therapy group and 13.2% in the delayed-therapy group, for a total duration of 6.5 years, with an accrual period of 1.5 years and a 5% annual loss to follow-up. The sample size of 1750 would also provide a power of 92% to show that early initiation of antiretroviral therapy provided at least a 20% reduction in the rate of serious clinical events associated with HIV-1 infection, which included death, a World Health Organization (WHO) stage 4 event, or a severe bacterial infection or pulmonary tuberculosis (primary clinical end point). By the end of the trial, we anticipated a total of 234 such clinical events, with cumulative incidence rates of 8.7% in the early-therapy group and 18.0% in the delayed-therapy group.

The study was reviewed twice each year by an independent NIAID multinational data and safety monitoring board. To guide the board in its recommendations regarding trial continuation, a composite monitoring end point was developed to include the occurrence of either death or WHO stage 4 events (excluding esophageal candidiasis) in HIV-1–infected participants or the transmission of HIV-1 to uninfected partners, whichever occurred first in the discordant couple. These were the events that were considered to have the greatest clinical effect on both the HIV-1–infected participant and the uninfected partner. A Lan–DeMets implementation of an O'Brien–Fleming monitoring boundary was used to evaluate the interim data with respect to this composite end point. An early termination would be indicated if there were conclusive evidence to rule out a hazard ratio of 0.80 or more in the early-therapy group. Interim analyses were planned when approximately 25%, 50%, 75%, and 100% of a total 340 composite events were observed.

We used the Kaplan–Meier method to calculate event-free probabilities and person-year analysis for incidence rate for a given year. We also used Cox regression to estimate relative risks, which were expressed as hazard ratios and 95% confidence intervals, and to provide adjustment for potential prognostic factors, such as the infected participant's baseline CD4 count, baseline plasma HIV-1 RNA concentration, and sex. The same Cox analyses were performed on linked transmissions, any transmissions, clinical events, and composite monitoring events. We used chi-square tests to compare the frequencies of adverse events. A P value of less than 0.05 was considered to indicate statistical significance. The cutoff was adjusted for multiple comparisons in trial-monitoring boundaries.

On April 28, 2011, the data and safety monitoring board recommended that the results of the study be released on the basis of data collection through February 21, 2011. At that time, 90% of couples remained enrolled in the study, with a median follow-up of 1.7 years; the total number of person-years of follow-up was 1585 in the early-therapy group and 1567 in the delayed-therapy group.

Results

Table 1. Baseline Characteristics of the Participants.*

Characteristic	HIV-1–Infected Participants		HIV-1–Uninfected Participants†	
	Early Therapy (N=886)	Delayed Therapy (N=877)	Early Therapy (N=893)	Delayed Therapy (N=882)
Demographic				
Female sex — no. (%)	432 (49)	441 (50)	441 (49)	418 (47)
Age group — no. (%)				
18–25 yr	145 (16)	161 (18)	154 (17)	174 (20)
26–40 yr	556 (63)	547 (62)	537 (60)	526 (60)
>40 yr	185 (21)	169 (19)	202 (23)	182 (21)
Education level — no. (%)				
No schooling	101 (11)	69 (8)	112 (13)	77 (9)
Primary schooling	360 (41)	347 (40)	317 (35)	344 (39)
Secondary schooling	346 (39)	388 (44)	373 (42)	367 (42)
Postsecondary schooling	79 (9)	72 (8)	91 (10)	93 (11)
Missing data	0	1 (<1)	0	1 (<1)
Marital status — no. (%)				
Single	49 (6)	38 (4)	53 (6)	43 (5)
Married or living with partner	833 (94)	833 (95)	834 (93)	833 (94)
Widowed, separated, or divorced	4 (<1)	6 (1)	6 (1)	6 (1)
Region — no. (%)				
North or South America	142 (16)	136 (16)	145 (16)	139 (16)
Asia	267 (30)	264 (30)	268 (30)	264 (30)
Africa	477 (54)	477 (54)	480 (54)	479 (54)
Sexual activity — no. (%)				
Any unprotected sex in past week	37 (4)	51 (6)	49 (5)	53 (6)
No. of sex partners in past 3 mo				
0–1	831 (94)	833 (95)	863 (97)	844 (96)
2–4	48 (5)	41 (5)	29 (3)	36 (4)
>4	7 (1)	2 (<1)	1 (<1)	1 (<1)
Missing data	0	1 (<1)	0	1 (<1)
No. of sexual encounters in past week				
0	246 (28)	225 (26)	253 (28)	240 (27)
1–2	430 (49)	438 (50)	410 (46)	433 (49)
3–4	156 (18)	158 (18)	180 (20)	151 (17)
>4	54 (6)	55 (6)	50 (6)	57 (6)
Missing data	0	1 (<1)	0	1 (<1)

STI at baseline 5% both arms

Circumcision rates 15% both arms

Condom use 100% in 95% individuals both arms

Results (continued)

Table 2. Incidence of Partner-Linked and Any HIV-1 Transmission and Clinical and Composite Events.

Variable	Early Therapy			Delayed Therapy			Hazard or Rate Ratio (95% CI)*
	Events	Person-yr	Rate (95% CI)	Events	Person-yr	Rate (95% CI)	
	no.		%	*no.*		%	
Linked transmission							
Total	1	1585.3	0.1 (0.0–0.4)	27	1567.3	1.7 (1.1–2.5)	0.04 (0.01–0.27)
1 yr	1	819.0	0.1 (0.0–0.7)	16	813.3	2.0 (1.1–3.2)	0.06 (0.00–0.40)
2–3 yr	0	686.5	0.0 (0.0–0.5)	9	682.8	1.3 (0.6–2.5)	0.00 (0.00–0.50)
>3 yr	0	79.9	0.0 (0.0–4.6)	2	71.2	2.8 (0.3–10.1)	0.00 (0.00–4.75)
Any transmission†							
Total	4	1585.3	0.3 (0.1–0.6)	35	1567.3	2.2 (1.6–3.1)	0.11 (0.04–0.32)
1 yr	2	819.0	0.2 (0.0–0.9)	18	813.3	2.2 (1.3–3.5)	0.11 (0.01–0.46)
2–3 yr	2	686.5	0.3 (0.0–1.1)	14	682.8	2.1 (1.1–3.4)	0.14 (0.02–0.62)
>3 yr	0	79.9	0.0 (0.0–4.6)	3	71.2	4.2 (0.9–12.3)	0.00 (0.00–2.16)
Clinical events‡							
Total	40	1661.9	2.4 (1.7–3.3)	65	1641.8	4.0 (3.1–5.0)	0.59 (0.40–0.88)
1 yr	29	831.0	3.5 (2.3–5.0)	39	832.6	4.7 (3.3–6.4)	0.75 (0.44–1.24)
2–3 yr	9	739.8	1.2 (0.6–2.3)	21	725.7	2.9 (1.8–4.4)	0.42 (0.17–0.96)
>3 yr	2	91.1	2.2 (0.3–7.9)	5	83.6	6.0 (1.9–14.0)	0.37 (0.04–2.24)
Composite events§							
Total	23	1700.1	1.4 (0.9–2.0)	79	1642.0	4.8 (3.8–6.0)	0.28 (0.18–0.45)
1 yr	13	843.7	1.5 (0.8–2.6)	47	833.9	5.6 (4.1–7.5)	0.27 (0.14–0.51)
2–3 yr	8	763.8	1.0 (0.5–2.1)	26	732.5	3.5 (2.3–5.2)	0.30 (0.12–0.67)
>3 yr	2	92.6	2.2 (0.3–7.8)	6	75.5	7.9 (2.9–17.3)	0.27 (0.03–1.52)

Results (continued)

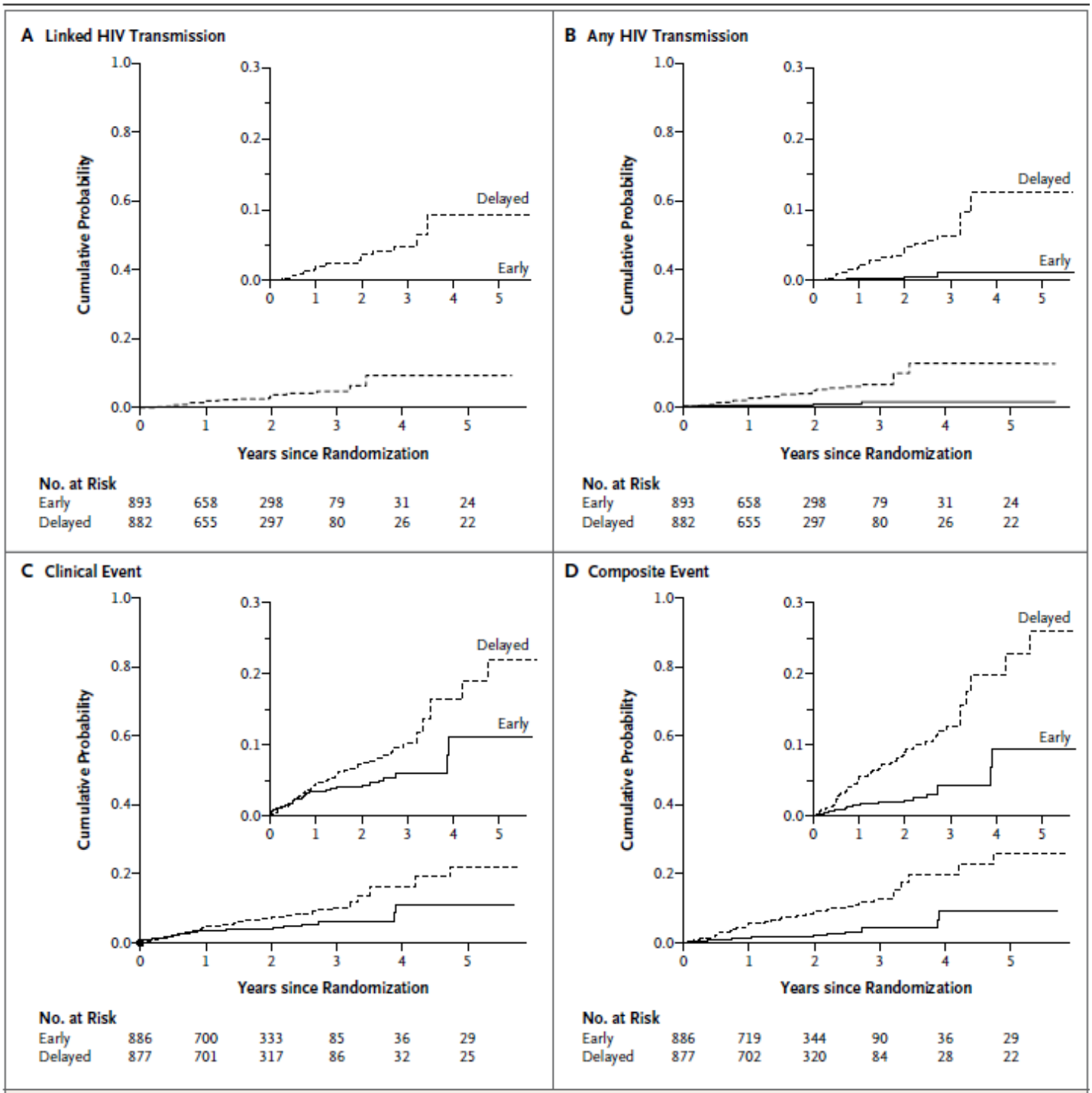

Figure 2. Kaplan–Meier Estimates for Partner-Linked and Any HIV-1 Transmission and for Clinical and Composite Monitoring Events.

Questions (percentage of marks)

1. Was the study ethical? (30%)
2. Was the design appropriate? (20%)
3. What were the key results? (30%)
4. What are the implications of the study? (20%)

End of paper