Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. B. Grinsztejn, MD and MS Cohen et al., the HPTN 052-ACTG Study Team

Background:

Best time to initiate ART to reduce progression of HIV-1 or non-AIDS clinical events unknown.

Early ART: Interim results after 1.7 years of fup showed a 96% reduction in HIV-1 transmission to a sexual partner and delayed time to AIDS events with early treatment (ART). Science: Breakthrough of the year 2011.

Compare effects of early and delayed ART on clinical outcomes.

Methods:

HPTN 052 trial, RCT, 13 sites, 9 countries: Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, USA, Zimbabwe.

Inclusion criteria: CD4 350–550 cells in HIV-1-infected persons (index case); no previous ART.

Early ART started at enrolment; delayed ART started either after 2 consecutive CD4 counts of 250 cell or less or after development of an AIDS-related illness.

Primary events: AIDS clinical events (WHO stage 4 HIV-1 disease, tuberculosis, and severe bacterial infections) and the following serious medical conditions unrelated to AIDS: serious cardiovascular or vascular disease, serious liver disease, end-stage renal disease, new-onset diabetes mellitus, and non-AIDS malignant disease. Analysis was by intention-to-treat.

Estimated time to first primary outcome with Kaplan-Meier, compared distributions by ART group with log-rank test. Distributions with cumulative event probabilities over 2 years (median fup).

Relative hazard of primary outcomes by prespecified sub groups (geographical region, sex, baseline CD4 count [<450 cells per µL vs ≥450 cells per µL]) using Cox proportional-hazards regression.

Data to May 11, 2011 (day before press release HPTN 052 study). 3 month's additional fup.

Findings:

N=1763; 886 early ART; 877 delayed ART. Median CD4 442 (IQR 373–522) early ART; 428 (357–522) delayed ART. Median fup 2.1 years (IQR 1.5–2.9).

Primary clinical events 57 early ART vs 77 delayed ART (hazard ratio 0.73, 95% CI 0.52–1.03; p=0.074). The cumulative probability of a primary outcome event over 2 years was 4.8% (95% CI 3.6–6.5) in the early ART group and 7.9% (6.2–10.1) in the delayed ART group.

New-onset AIDS events in 40 participants early ART vs 61 delayed ART (0.64, 0.43–0.96; p=0.031). The cumulative probability of having an AIDS event over 2 years was 3.3% (2.4–4.9) in the early ART group compared with 6.0% (4.5–7.9) in the delayed ART group.

Tuberculosis 17 vs 34 patients, respectively (0.49, 0.28–0.89, p=0.018). Cumulative probability of tuberculosis events over 2 years was 1.2% (0.6–2.2) in patients with early ART group and 3.7% (2.5–5.3) in those with delayed ART.

26 people died, 11 early ART and 15 delayed ART.

In total, 498 primary and secondary outcomes early cART (incidence 24.9 per 100 person-years, 95% CI 22.5–27.5) vs 585 delayed ART (29.2 per 100 person-years, 26.5–32.1; p=0.025).

Multivariable analysis, a higher risk was noted: with older age (p=0.017), higher baseline HIV-1 RNA titre (p=0.013), an amount of hemoglobin < than 85 g/L (p=0.025), and hepatitis B virus co-infection (p=0.040). A proximal (time-updated) increase in CD4 cells of 50 cells per µL associated with a 10% lower hazard of a primary outcome (HR 0.90, 95% CI 0.85–0.95; p=0.001.

Delayed ART group began ART after a median time of 3.8 years from enrolment (95% CI 3.5–4.4; Fig 5A), with a median CD4 count of 230 cells per µL (IQR 197–249) and median HIV-1 RNA of 5.0 log10 c/mL (IQR 4.5–5.5). Predominantly combination of zidovudine, lamivudine, and efavirenz. CD4 course.

Primary and secondary endpoints not among participants with low CD4 counts; Most outcome events recorded when most recent CD4 count higher than 350 cells/µL. Median CD4 count for primary clinical events 353 cells/µL (IQR 301–425) in patients assigned to delayed ART compared with 502 cells per µL (417–653) in participants allocated to the early ART.

Discussion:

HIV Prevention Trials Network (HPTN) 052 first RCT to directly compare early versus delayed ART in HIV-1 infected adults with CD4 counts of 350–550 cells/µL.

Findings show that early ART delayed the time to AIDS events, tuberculosis, and WHO stage 2 and 3 events and significantly reduced the incidence of these events, compared with patients for whom ART was delayed until CD4 cell counts reached less than 250 cells per μL. Early ART led to a rapid rise in CD4 cells to near normal levels. Our results, combined with the striking reduction in risk of HIV-1 transmission resulting from suppression of HIV-1 replication, provide strong support for early initiation of ART.

Funding: US National Institute of Allergy and Infectious Diseases.