

TB/HIV Co-infection: Summary of Major Studies and Considerations for 2009 ART Guidelines Review

ART for all HIV-infected TB patients regardless of CD4 count

1. When to initiate ART in HIV-infected TB patients in terms of CD4 threshold (table 1)

Several observational studies showed benefits on mortality and morbidity when ART is initiated earlier in HIV-infected populations, but there is no RCT comparing at what CD4 threshold to initiate ART among HIV-infected TB patients.

The CIPRA trial conducted in Haiti among HIV-infected patients showed that the early start of ART, at CD4 count between 200 and 350 cells/mm³ (early treatment group) improves survival compared to deferring treatment until CD4 count drops <200 cells/mm³ (standard-of-care group). There were nearly four times as many deaths in the standard-of-care group (23 deaths) compared to the early treatment group (six deaths). Among participants who began the study without TB, 36 in the standard-of-care group developed TB compared to 18 people in the early treatment group. These results were statistically significant.

Several observational studies conducted in high income countries showed benefits on mortality and morbidity when ART is initiated at high CD4 level:

Modeling studies reported that early initiation of ART in the course of HIV infection, high population coverage with ART and high compliance levels would be needed to effectively reduce the number of TB cases and TB mortality rates (1, 2). Universal HIV testing with immediate initiation of ART would reduce HIV incidence and mortality to less than 1 case per 1000 people within ten years of implementation of universal and prompt antiretroviral therapy, which could potentially impact the incidence of TB (3).

2. When to initiate ART in HIV-infected TB patients after the start of TB therapy (table 2)

The SAPIT trial conducted in South Africa showed, in interim analysis, that mortality rates were significantly higher among patients who initiated antiretroviral therapy after completion of TB treatment (11.6 per 100 person-year) compared to patients who started within the first two months of intensive phase or after completing the intensive phase of TB therapy (5.1 per 100 person-year) (4). An estimated 10,000 deaths could be prevented every year by the initiation of ART in HIV-infected TB patients with CD4 <500/mm³.

Results from observational studies favour the early start of ART in HIV-infected TB patients receiving TB treatment. A study in Spain showed that starting antiretroviral therapy in the first two months of TB treatment was an independent predictor of survival when compared to an initiation after three months of TB treatment (5). Similarly, the risk of death increased the longer antiretroviral therapy was delayed in Thailand (6).

In a retrospective study in South African, starting antiretroviral therapy within the first 30 days of TB treatment did not increase mortality (7). A retrospective study in Iran showed that improved survival among hospitalized HIV-infected TB patients with CD4 <100 was associated with the earlier initiation of ART (8).

3. Additional information from observational studies to favour ART for all HIV-infected TB patients in resource-limited settings

Many observational studies conducted in resource-limited settings have described high mortality rates among HIV-infected TB patients. TB case fatality rates in Africa are 16-35% among HIV-infected patients not receiving ART and 4-0% among HIV-negative individuals (9).

The risk of clinical deterioration and death during TB treatment in HIV-infected patients has been associated with low CD4 count at TB diagnosis (10).

The use of ART has been associated with significant reductions in mortality risk up to 95% in adjusted analysis (11) (table 3).

In addition, ART significantly reduces TB incidence rates by up to 90% at individual level (11) (table 4) and by 60% at population level (12). ART also reduces TB recurrence rates by 50% (13).

The long-term risk of people living with HIV for developing active TB was also found to be correlated to the time that patients spend at CD4 count below 500 cells/mm³ (14).

ART should be provided to all HIV-infected TB patients in resource-limited settings regardless of CD4 count given:

- ✓ The high mortality rates among HIV-infected TB patients, the survival benefit of ART and the decreased risk of TB at individual level, as well as the impact on TB control at population level;
- ✓ There is no RCT to give strong recommendations on the CD4 threshold to initiate ART in HIV-infected TB patients;
- ✓ The convergence of results and findings from observational and modeling studies.

What to start in HIV-infected TB patients receiving rifampicin

1. Comparison of nevirapine and efavirenz for rifampicin co-administration (table 5)

A randomized controlled trial comparing standard doses of efavirenz and nevirapine-based ART in HIV-infected TB patients receiving rifampicin demonstrated that 600 mg efavirenz once daily was adequate for suppression of HIV viral load despite interpatient variability in serum drug concentrations (15). Nevirapine at the standard dose of 200 mg twice daily was effective in achieving viral load suppression although efavirenz was superior.

Previous observational studies provided conflicting results about the efficacy of efavirenz and nevirapine administered with and without rifampicin:

- ✓ A cohort study in Botswana showed no difference in immunological and virological outcomes throughout the first year of efavirenz and nevirapine-based ART co-administered with or without rifampicin (16).
- ✓ In contrast, patients in South Africa had less favourable virological outcomes when they started nevirapine while already receiving rifampicin-based TB treatment compared to those who had started efavirenz after rifampicin (17). Similarly, they had poorer virological outcomes compared to those who initiated TB treatment while already receiving nevirapine or efavirenz-based antiretroviral therapy.

All these studies had a short follow-up period for measuring antiviral activity. No studies have investigated the use of efavirenz short term while taking rifampicin-based regimen for TB disease and switching back to nevirapine after completion of TB treatment.

Reports of safety and tolerability of these therapeutic regimens varied across observational studies: while there was no difference in adverse events between nevirapine and efavirenz when given with rifampicin in some studies (16, 17), higher rates of hepatotoxicity due to nevirapine were observed in others (18).

2. Use of nevirapine with rifampicin

Randomized trials and observational cohorts have reported that concomitant use of rifampicin leads to short-term sub-therapeutic nevirapine plasma concentrations (17, 19-22). However, results about the consequences on virological suppression are conflicting. Thai patients receiving nevirapine alone vs. nevirapine and rifampicin showed similar virological outcomes at 144 weeks (23). Excess virological failures (HIV-RNA ≥ 400 copies/mL) at 18 months were observed in South African patients receiving rifampicin at the start of nevirapine treatment compared to patients on nevirapine alone (17)

3. Triple nukes

Triple nucleoside reverse transcriptase inhibitor regimens ("triple nukes") for first line HIV therapy avoid the interaction between non-nucleoside reverse transcriptase inhibitors and rifampicin. One observational study investigated the triple nucleoside reverse transcriptase inhibitor regimen abacavir, zidovudine, lamivudine in HIV-infected TB patients and reported that virological success (HIV-RNA < 50 copies/mL) was achieved in 76% of patients at 24 weeks with no hypersensitivity reaction (24).

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Table 1: Benefit on mortality and morbidity of early initiation of ART vs. deferring ART in TB-HIV-infected patients

Study	Study site	Design	Sample size	Main results
CIPRA HT 001 (Fitzgerald et al. IAS 2009)	Haiti	RCT: - Early start of ART with CD4 count between 200-350 (early treatment group) - Deferring ART until CD4 drops <200 or development of an AIDS defining illness (standard-of-care group)	816 adults randomized into the 2 arms	- The deferring arm was stopped by DSMB in May 2009 - Improved survival in early treatment group with 6 deaths in this group vs. 23 deaths in the standard-of-care group - Decreased risk of TB in early treatment group with 18 patients without TB at enrolment who developed TB in early treatment group compared to 36 in standard-of-care group.
Currie et al, AIDS.2003 17(17):2501	Using data from Kenya and Uganda	Modelling study		ART can be effective in minimizing the number of TB cases and deaths with high levels of coverage and compliance
Atun et al, Int J STD AIDS. 2007, 18(4):267		Modelling study		High population coverage with ART (75% or higher) is required to substantially reduce the number of deaths due to TB.

Table 2: Time to ART initiation in HIV-infected TB patients after TB therapy

Study	Study site	Design	Sample size	Main results
SAPIT	South Africa	RCT: After initiation of TB therapy, start ART - <2 weeks = "early integrated arm" - > 2months = "delayed integrated arm" - after completion of TB treatment "delayed arm"	645	-The sequential arm was stopped by DSMB in September 2008 - Mortality rate per 100 PY: Integrated arm (pooled): 5.1 (431 patients, 24 deaths) Sequential arm: 11.6 (214 patients, 26 deaths) P=.005, benefit were seen for patients with CD4<200 and those with CD4 200-500.
Velasco, JAIDS 2009; 50:148	Spain	Cohort study, partially retrospective and partially prospective	313	Starting ART in the first two months of TB treatment was an independent predictor of survival (HR: 0.37, 95% CI 0.17-0.66) when compared to an initiation after three months of TB treatment
Varma, BMC 2009; 9:42	Thailand	Prospective cohort study	667	Risk of death increased the longer ART was delayed: HR 9.0, 95% CI 1.1-73.0 for those for whom ART was delayed compared to those who initiated ART within the first 120 days of TB treatment.
Westreich, AIDS 2009; 23:707	South Africa	Retrospective cohort study	7512	Starting ART within the first 30 days of TB treatment did not increase mortality (HR 1.28, 95%CI 0.78-2.10) compared to 31-60 days (HR: 1.08, 95%CI 0.59-1.98), 61-120 days (HR:0.89, 95%CI 0.48-1.63) and >120days (HR: 1.25, 95%CI 0.65-2.43).
Tabarsi, Journal of the International AIDS Society 2009; 12:14	Iran	Retrospective cohort study	69	Death occurred more frequently in patients with CD4 count <200 starting ART after 8 weeks of TB treatment (27.7%) compared to patients with CD4 count <100 starting ART 2 weeks after TB treatment or patients with CD4 count 101-200 starting ART after 8 weeks of TB treatment (4.5%) P=0.03.

Table 3: Observational cohort studies (n=8) showing the impact of ART on mortality among patients with HIV-associated TB*

Study	Country	Study design	Outcome
Dheda et al. 2004 [65]	United Kingdom	Retrospective study of HIV-TB patients (n=99) treated in pre-ART era and in ART era.	Adjusted hazards of death or new AIDS defining illness was 0.34 (95%CI, 0.18-0.63) during ART era
Manosuthi et al. 2006 [66]	Thailand	Retrospective cohort study (n=1003) comparing mortality in a historical natural history cohort with rates in an ART cohort	The adjusted hazards of death associated with use of ART was 0.05 (95%CI, 0.02-0.12).
Akksilp et al. 2007 [67]	Thailand	Prospective cohort (n=329) comparing patients receiving and not receiving ART	Adjusted hazards of death was 0.2 (95%CI, 0.1-0.4)
Zachariah et al. 2007 [43]	Malawi	Retrospective observational cohort in which a proportion of patients started ART during the continuation phase of TB treatment (n=658)	No difference in mortality between patients who chose or did not choose to receive ART, but potential allocation bias according to degree of immunodeficiency and most deaths occurred pre-ART during intensive phase.
Nahid et al. 2007 [49]	United States	Retrospective observational cohort (n=264) 1990-2001 spanning pre-ART and ART era	Use of ART protected against mortality compared with patients who did not receive ART (hazard ratio 0.36, 95% CI 0.14-0.91)
Haar et al. 2007 [42]	Netherlands	Retrospective observational study of national data 1993-2001 spanning pre-ART and ART era	Compared to 1993-1995, adjusted odds of death during 1999-2001 was 0.46 (95%CI, 0.24-0.89) while no such change was observed among HIV-uninfected TB patients.
Varma et al. 2009 [68]	Thailand	Prospective multi-centre observational study (n=667) comparing patients receiving and not receiving ART	Adjusted hazards of death among those who received ART was 0.16 (95%CI, 0.07-0.36)
Velasco et al. 2009 [69]	Spain	Retrospective observational cohort 1987-2004 (n=313) comparing patients receiving and not receiving ART	Compared to no ART, initiation of ART within the first 2 months of TB treatment was associated with an adjusted hazards of death of 0.37 (95%CI, 0.17-0.66)

* From Lawn et al, *Antiretroviral Therapy for Control of the HIV-associated Tuberculosis Epidemic in Resource-Limited Settings, Clinics in Chest Medicine (in press)*.

Table 4: Studies (n=8) reporting the impact of ART on TB incidence rates in observational cohorts*

Study	Setting	N	Study period	Study design	Impact of ART on TB incidence rates	Adjusted hazards ratio (95% CI)
A. Studies comparing TB rates in cohorts before and after introduction of ART						
Brodt et al. 1997 [56]	Germany	1003	1992-1996	Cohort of homosexual men 1992-1996	No change in overall cohort incidence rates (range, 2.1-2.7 cases/100PYs)	-
Kirk et al. 2000 [57]	Europe	6,972	1994-1999	EuroSIDA multicentre cohort 1994-1999	Overall rate in cohort decreased from 1.8 to 0.3 cases/100PYs	-
B. Studies comparing TB rates in patients receiving or not receiving ART						
Ledergerber et al. 1999 [17]	Switzerland	2410	1995-1997	Swiss HIV Cohort Study	Rate 0.78 cases/100 Pys pre-ART and 0.22 cases/100PYs with first 15 months ART	-
Jones et al. 2000 [11]	United States	-	1992-1998	Multicentre cohort. Adult/Adolescent Spectrum of HIV Disease (ASD) project	Steep decreases in TB incidence rates	0.2 (0.1-0.5)
Girardi et al. 2000 [58]	Italy	1360	1995-1996	Multicentre cohort	Not stated	0.08 (0.01-0.88)
Santoro-Lopes et al. 2002 [59]	Brazil	255	1991-1998	Prospective cohort	Not stated	0.2 (0.04-1.13)
Badri et al. 2002 [12]	South Africa	1034	1992-2001	Rates compared in separate prospective observational cohorts receiving or not receiving ART	Markedly lower TB rates across a broad spectrum of baseline CD4 counts and WHO stage	0.19 (0.09-0.38)
Golub et al. 2007 [40]	Brazil	11,026	2003-2005	Multicentre retrospective cohort	Rates among those receiving and not receiving ART were 1.9 and 4.0 cases/100PYS, respectively	0.46 (0.33-0.63)
Miranda et al. 2007 [60]	Brazil	463	1995-2001	Multicentre retrospective study	Rates among those receiving and not receiving ART were 1.2 and 13.4 cases/100PYS, respectively	0.2 (0.1-0.6)
Muga et al. 2007 [61]	Spain	2238	1980s-2004	Multicentre seroconverter cohort	Marked reduction in rates after 1995 in all HIV transmission categories	0.31 (0.17-0.54)
Moreno et al. 2008 [62]	Spain	4268	1997-2003	Multicentre hospital-based cohort	Rates among those receiving and not receiving ART were 0.5 and 1.6 cases/100PYs, respectively	0.26 (0.16-0.40)
Golub et al. 2009	South Africa	2778	2003-2007	Retrospective data from two study sites	Rates among those receiving and not receiving ART were 4.6 and 7.1 cases/100PYs, respectively	0.36 (0.25-0.51)

* From Lawn et al, *Antiretroviral Therapy for Control of the HIV-associated Tuberculosis Epidemic in Resource-Limited Settings, Clinics in Chest Medicine (in press)*.

Table 5: Comparison of nevirapine and efavirenz for rifampicin co-administration

Study	Study site	Design	Sample size	Main results
Manusothi, CID 2009; 48:1752	Thailand	RCT	142 randomized to receive EFV or NVP	- 73.2% in the EFV group as compared to 71.8% in the NVP had HIV-RNA<50 copies/ml at week 48, P>0.05 - No difference in toxicity
Shipton, IJTLD 2009; 13:360	Botswana	Retrospective cohort	- 155 in ART-alone group (NVP or EFV) - 155 in TB treatment-exposed group	- At 12 months, 82% in the ART-only group and 91% in the TB treatment -exposed group had HIV-1 RNA<400 copies/ml (P=0.28) - Trend towards more hepatotoxic events in the TB treatment-exposed group compared to ART-alone group (9% vs. 3%, P=0.05)
Boulle, JAMA 2008; 300:530	South Africa	Prospective cohort	-1074 EFV+ RFP - 961 EFV alone - 209 NVP + RFP - 1726 NVP alone	- Higher virological failure (up to 18 months FU) among patients starting NVP while already on RFP-based TB therapy: OR: 1.7, 95% CI 1.2-2.6) when compared to patients receiving NVP alone (without RFP). - Similar virological outcomes among patients starting NVP while already on RFP-based TB therapy compared to those starting RFP while already receiving NVP (OR 1.0, 95%CI 0.5-2.0) and when compared to those taking EFV with or without concurrent RFP (OR 1.1, 95% CI 0.8-1.5) - No difference in toxicity
Manosuthi, HIV medicine 2008, 9:294-99	Thailand	Retrospective cohort	- 77 EFV +RFP -111 NVP+ RFP	- At 48 weeks, 77.9% in the EFV group and 67.9% in the NVP group achieved HIV-1 RNA<50 copies/ml - No patient in the EFV group and 7.2% in the NVP group discontinued ART because of adverse reactions (p=0.084).