NORTHWEST AIDS EDUCATION AND TRAINING CENTER

HIV/TB Co-infection: Initial Management

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Presenter
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NW AETC | echo

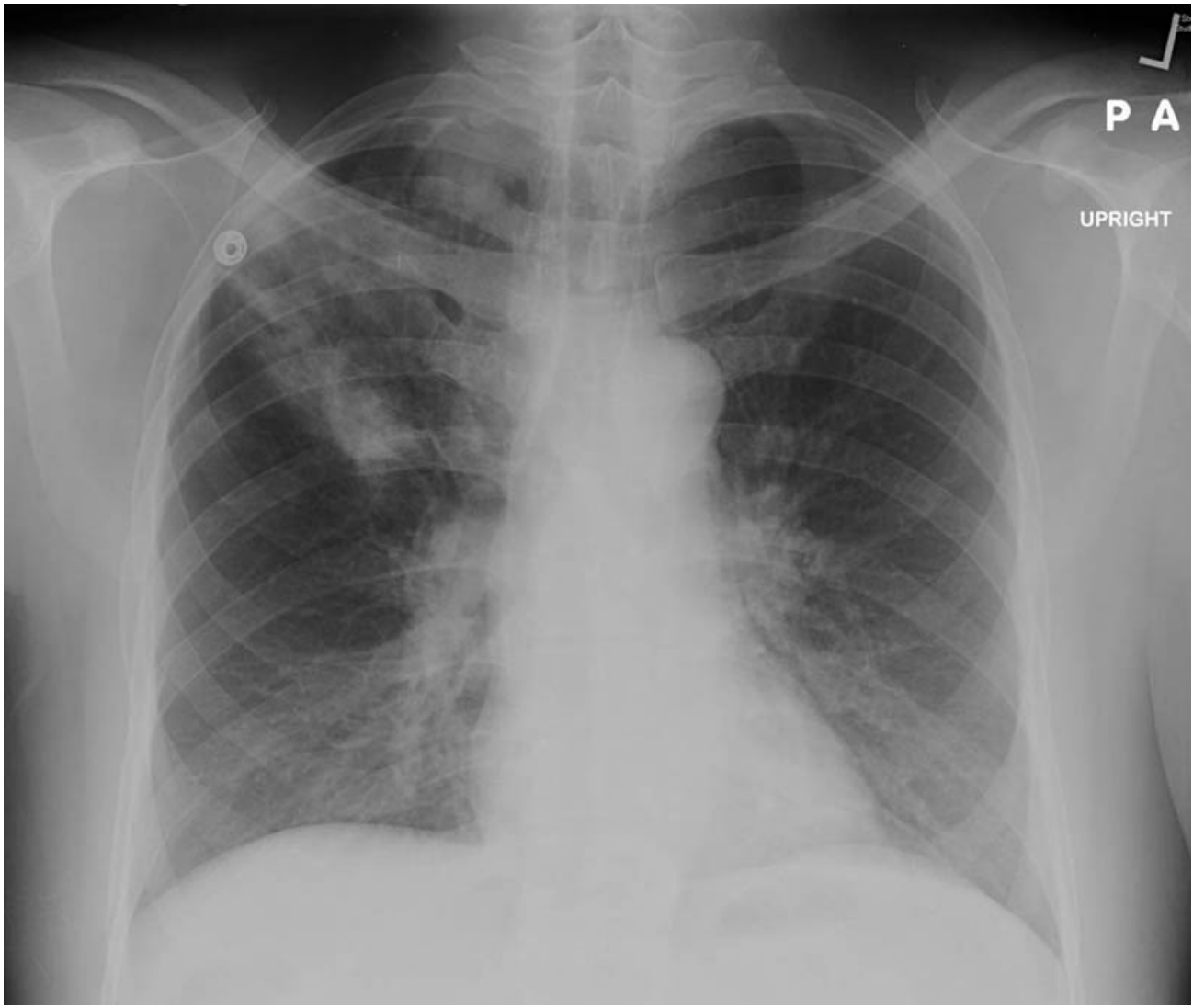
Case

Case

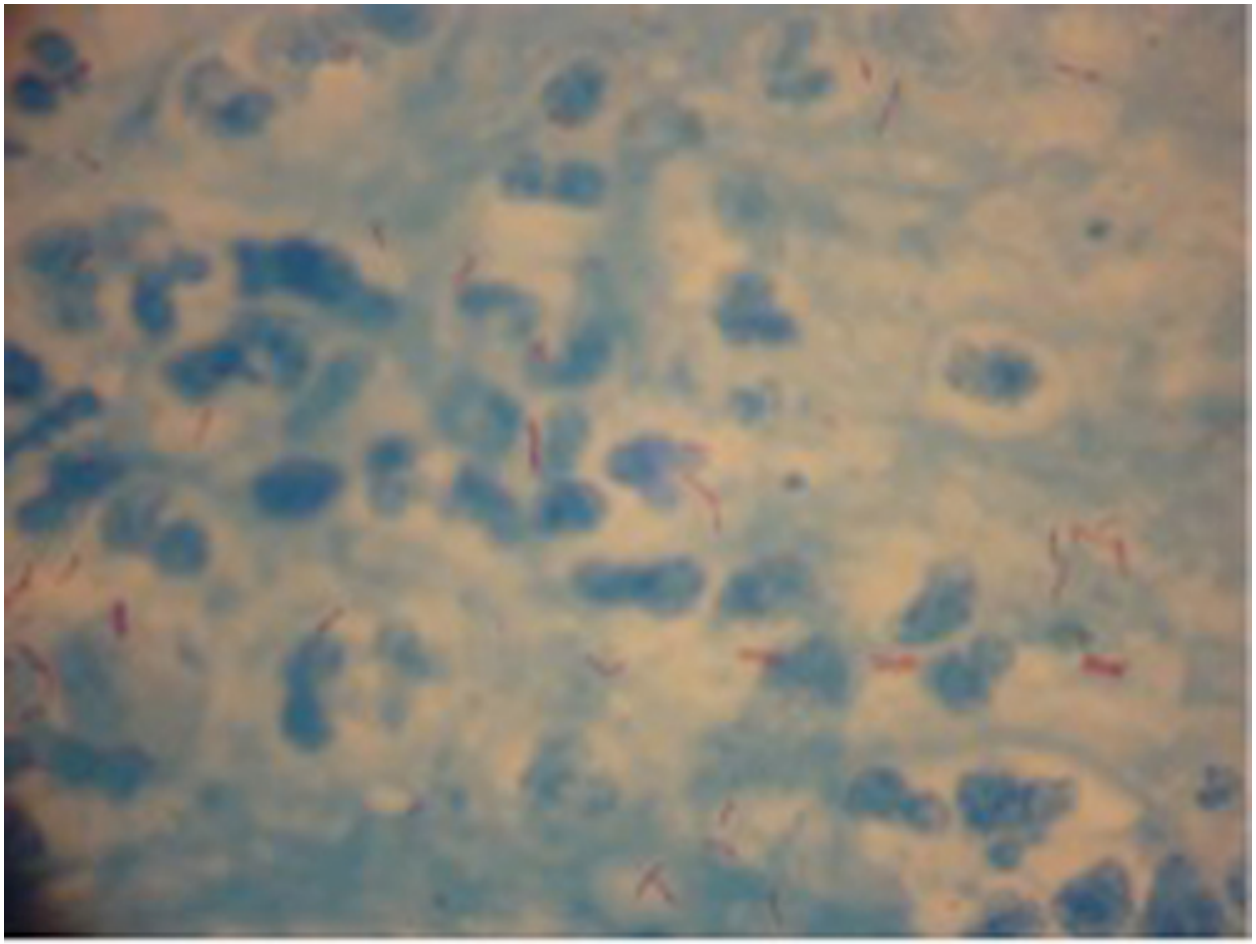
- A 40-year-old man presents to the Emergency Department with a 2-month history of fever, night sweats, weight loss, and cough.
- VS: tachypneic at 20 resp/minute; SaO2 93% on RA
- PE: cachectic; crackles in right lung field
- PMHx: remarkable only for HIV disease. Last known CD4 count, from 3 years ago, was 220 cells/mm3, with an HIV viral load at that time of 67,000 copies/mL. Not on antiretroviral therapy.
- Medications: none
- Social Hx: immigrated from Ethiopia 3 years ago and was lost to follow-up after his first health care encounter.
- What conditions are you worried about?
- What tests would you order?

Case continued

- You order a CXR, sputum smear, and labs
- WBC 2.3
- Hgb 9.2
- Platelets 132



Case: Sputum Smear



Source: Dr Desalew Mekonnen, University of Gondar, Ethiopia

Case continued

- He is admitted with respiratory precautions and supplemental oxygen
- Sputum cultures & sensitivities pending
- What is your next management step?
  A. Start anti-tuberculosis therapy with rifampin, isoniazid, pyrazinamide and ethambutol
  B. Start antiretroviral therapy; start TB therapy if/when TB is confirmed by molecular probe assay with sensitivity analysis
  C. Start PCP prophylaxis; start TB therapy if/when TB is confirmed by molecular probe assay with sensitivity analysis
  D. Start corticosteroids to prevent immune reconstitution inflammatory syndrome (IRIS) once treatment for HIV/TB is started

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Case: 40 yo man with AIDS, pulmonary TB

- You initiate anti-TB therapy with rifampin, isoniazid, pyrazinamide and ethambutol
- Additional labs return the next day:
  - Molecular assay confirms M.tb without evidence of resistance
  - Absolute CD4 count 23 (4%)
  - HIV viral load 189,000 copies/mL
- What should be done regarding Pneumocystis Pneumonia (PCP) prophylaxis?
  A. Defer PCP prophylaxis until two months of TB therapy is completed
  B. Start PCP prophylaxis with TMP-SMX
  C. Start PCP prophylaxis with atovaquone
  D. Start PCP prophylaxis with aerosolized pentamidine

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Case: 40 yo man with AIDS, pulmonary TB

- When should antiretroviral therapy for HIV be started for this patient?
  A. Now (at the same time as PCP prophylaxis is started)
  B. As soon as he is tolerating TB therapy (within 2 weeks)
  C. After he completes the first two months (intensive phase) of TB therapy
  D. After he completes the full course of TB therapy

When Should Antiretroviral Therapy be Started for HIV-infected patients with TB?

THE SAPIT, CAMELIA, AND STRIDE STUDIES

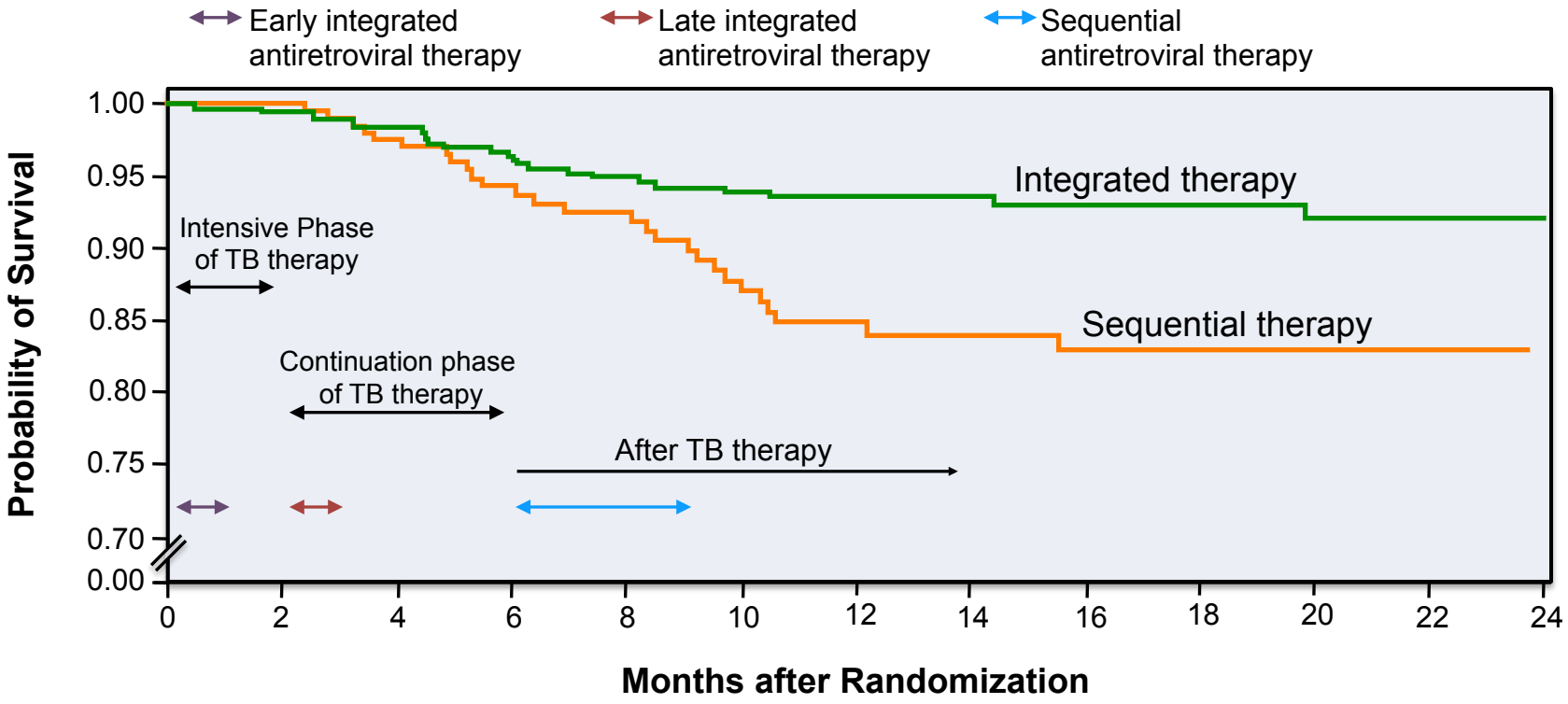
SAPIT: South Africa

- The SAPIT trial randomized 642 South African HIV-infected adults with active TB and a CD4 count less than 500 cells/mm^3 to initiate antiretroviral therapy at one of three time intervals following initiation of TB therapy.
- For the TB therapy, patients were scheduled to take four anti-TB drugs for the initial 2-months (intensive phase), followed by two anti-TB drugs for 4 months (continuation phase).
- The “integrated therapy” group initiated antiretroviral therapy during their treatment for TB infection, either within 4 weeks of initiation of TB therapy (the “early integrated therapy” group) or within 4 weeks of completing the initial 2 months of TB therapy (the “late integrated therapy”) group.
- The “sequential therapy” group deferred initiation of antiretroviral therapy until completion of TB therapy.

N Engl J Med. 2010;362:697-706.

Figure d03

Kaplan-Meier Survival Curves from the SAPIT Study Comparing Mortality among Patients in the Integrated versus the Sequential Therapy Groups



Source: Salim S. Abdool Karim, et al. N Eng J Med 2010; 362:697-706.

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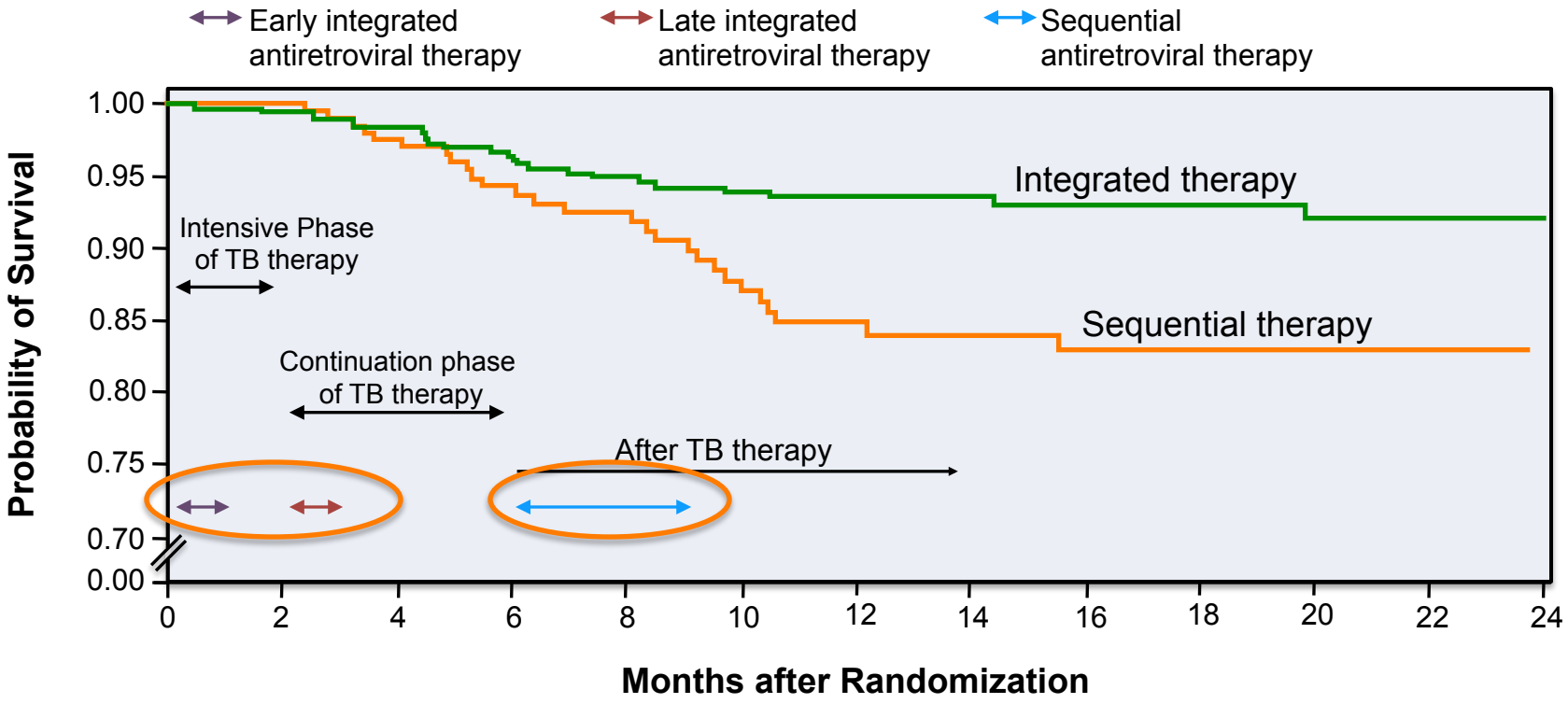

Source: Salim S. Abdool Karim, et al. N Eng J Med 2010; 362:697-706.

What about patients who started therapy “Early” vs “Late” in the Integrated Therapy arm of the SAPIT trial?

EARLY THERAPY: STARTED ART WITHIN 4 WEEKS OF STARTING TB THERAPY

LATE THERAPY: STARTED ART 8-12 WEEKS AFTER STARTING TB THERAPY

Figure d03

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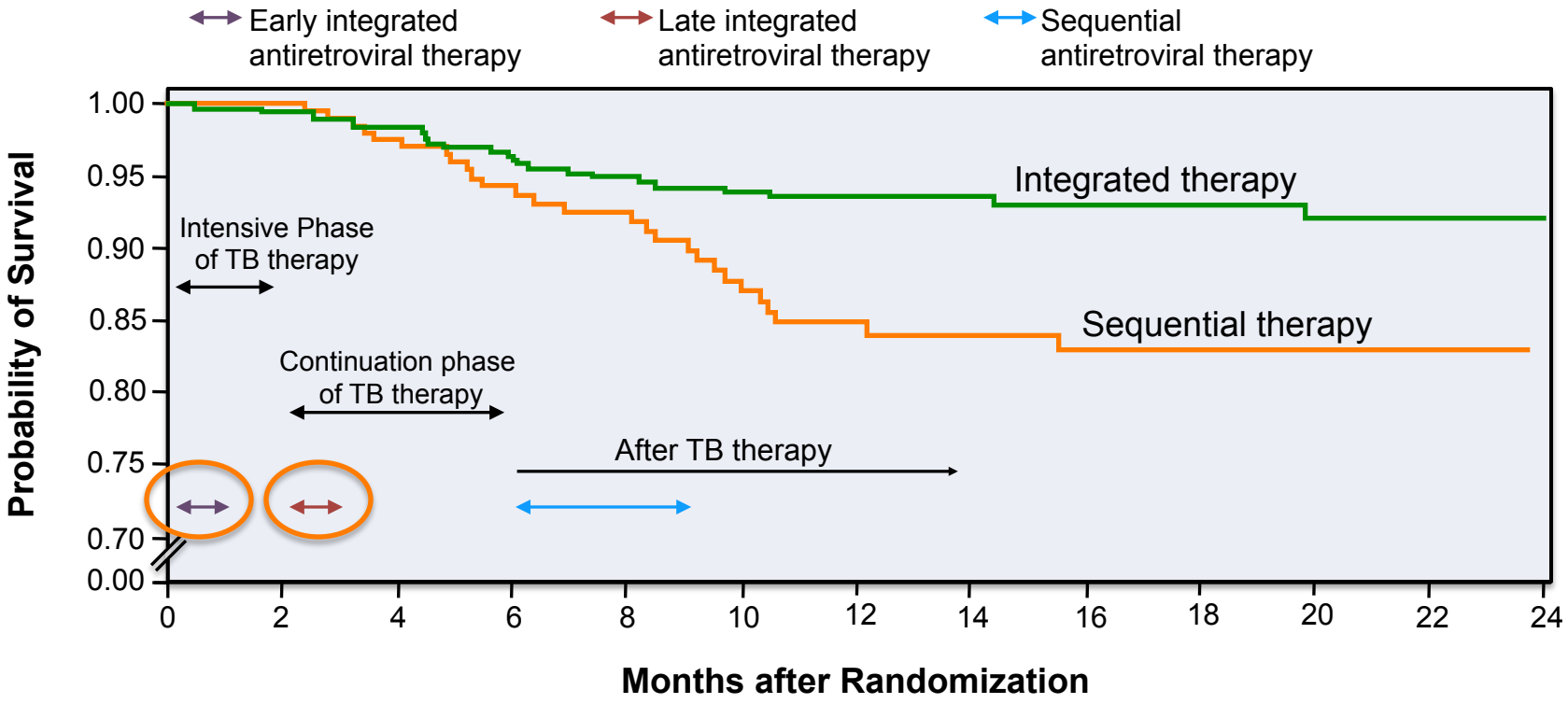
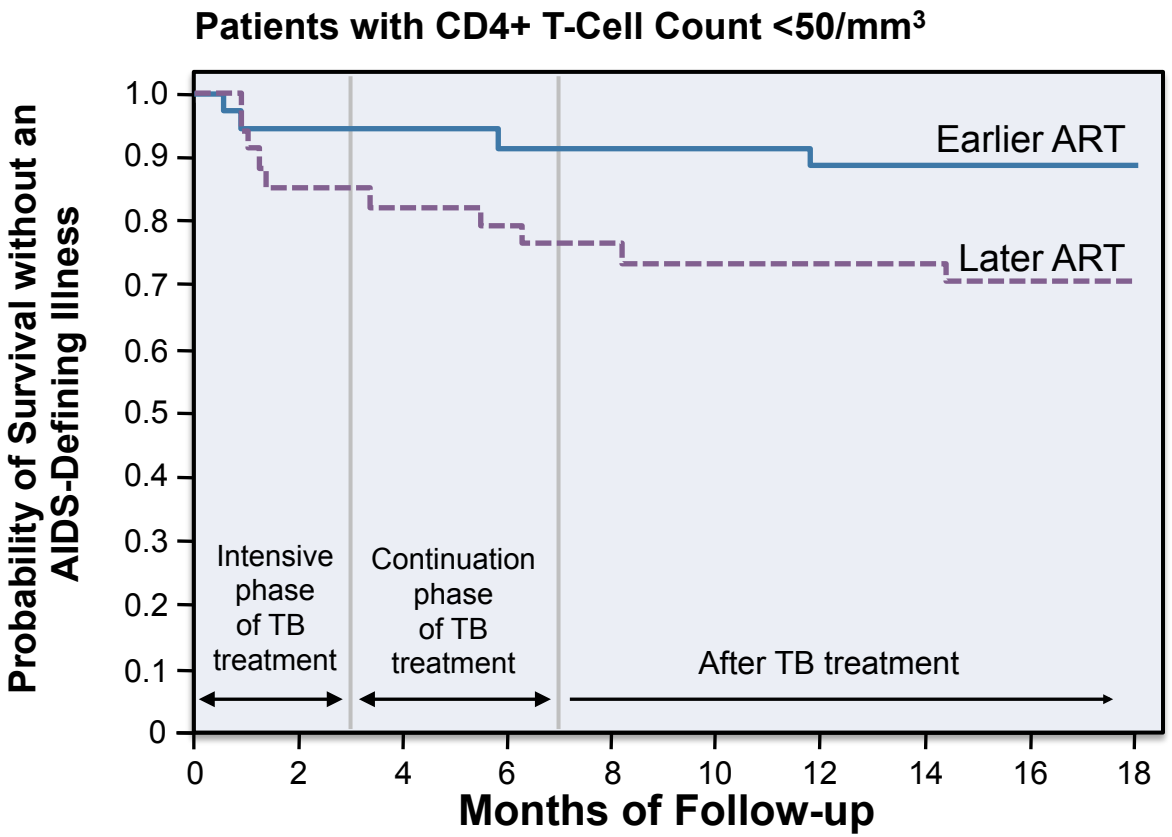


Source: Salim S. Abdool Karim, et al. N Eng J Med 2010; 362:697-706.

Figure d04a

Kaplan–Meier Curves for Survival without an AIDS-Defining Illness from the SAPIT Trial

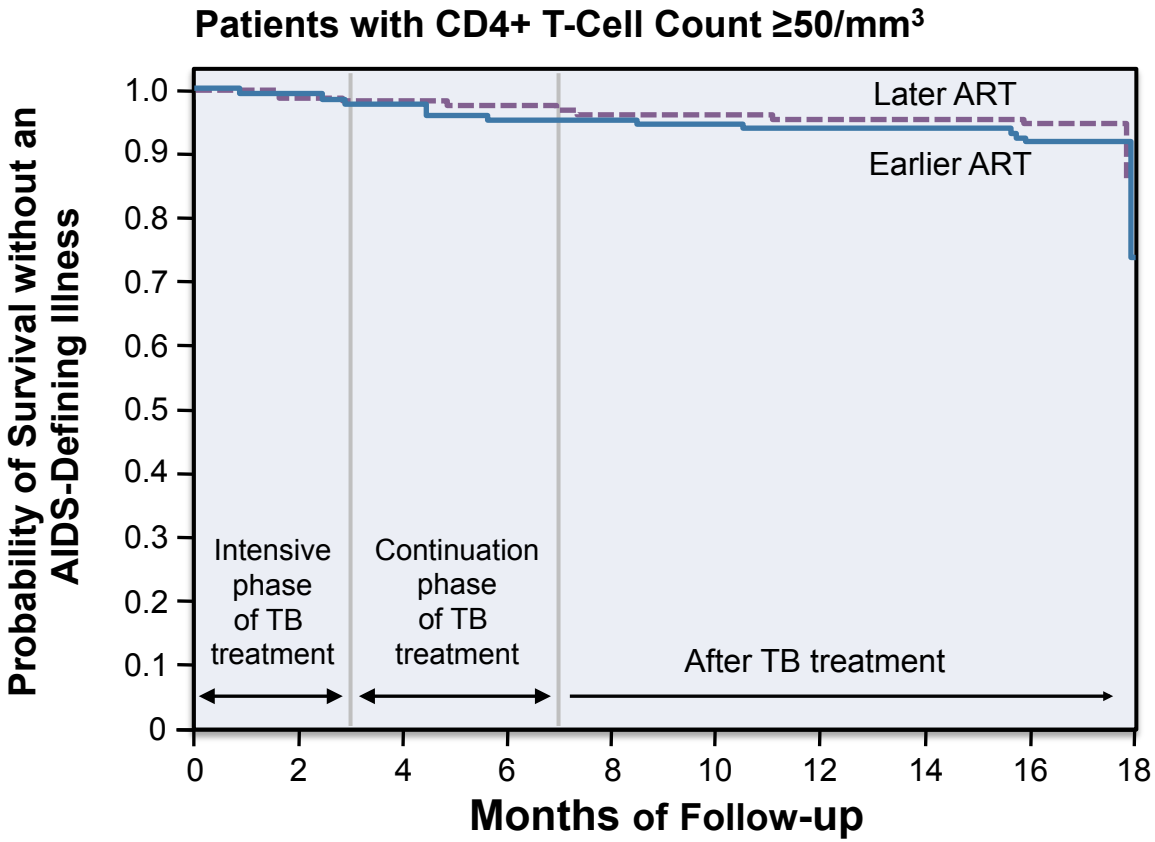


No. at Risk										
Earlier ART	37	33	33	32	32	32	31	31	31	29
Later ART	35	29	28	27	26	24	24	24	23	21

Source: Abdool Karim SS, et al. N Eng J Med 2011;365:1492-501.

Figure d04b

Kaplan–Meier Curves for Survival without an AIDS-Defining Illness from the SAPIT Trial



No. at Risk										
Earlier ART	177	166	159	149	145	140	137	133	125	121
Later ART	180	164	153	148	138	134	129	126	124	119

Source: Abdool Karim SS, et al. N Eng J Med 2011;365:1492-501.

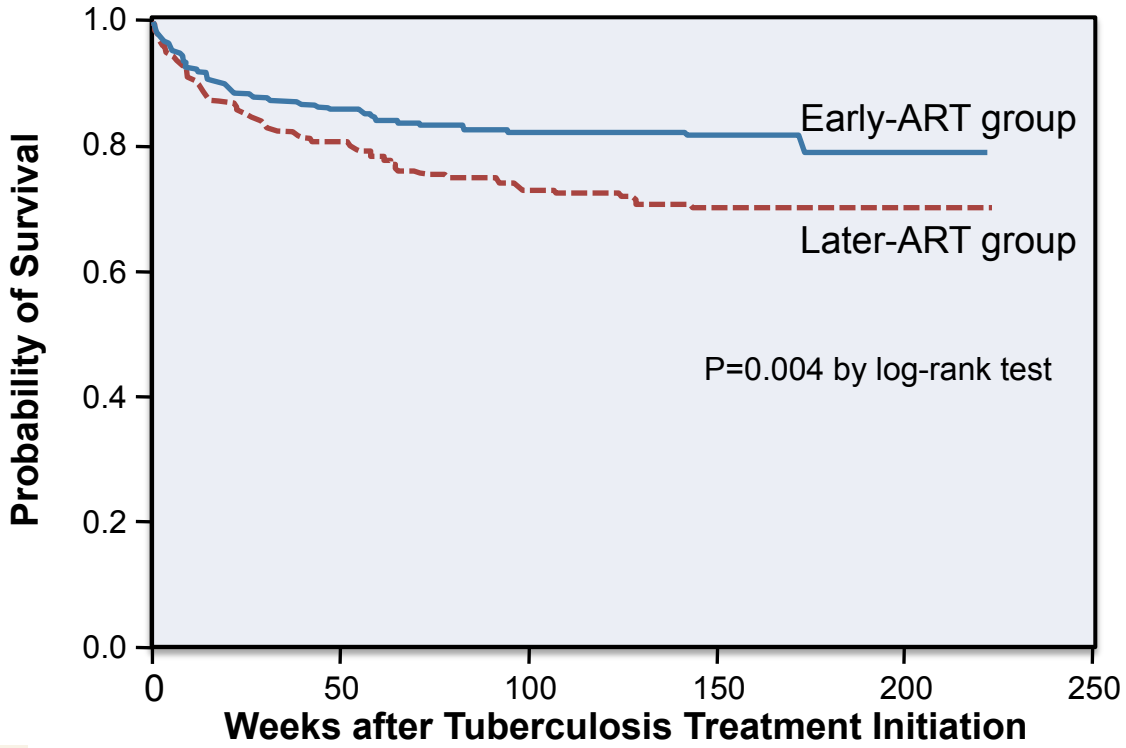
CAMELIA: Cambodia

- open label, randomized trial that compared clinical outcomes associated with initiation of antiretroviral therapy at 2 weeks versus 8 weeks following initiation of TB therapy for patients with confirmed TB disease.
- 661 Cambodian HIV-infected patients with an absolute CD4 count less than 200 cells/mm^3 initiated standard TB therapy (planned 6 months of treatment) and were randomized to initiate antiretroviral therapy either
  - at week two of TB therapy (the “Early ART” arm); OR
  - at week eight of TB therapy (the “Later ART” arm).

N Engl J Med. 2011;365:1471-81

Figure d05

Kaplan–Meier Survival Estimates According to Study Group.



No. at Risk					
Early-ART group	332	278	192	101	4
Later-ART group	329	256	168	87	3
No. of Deaths					
Early-ART group	0	46	56	57	59
Later-ART group	0	63	85	90	90

Source: Blanc FX, et al. N Eng J Med. 2011;365:1471-81.

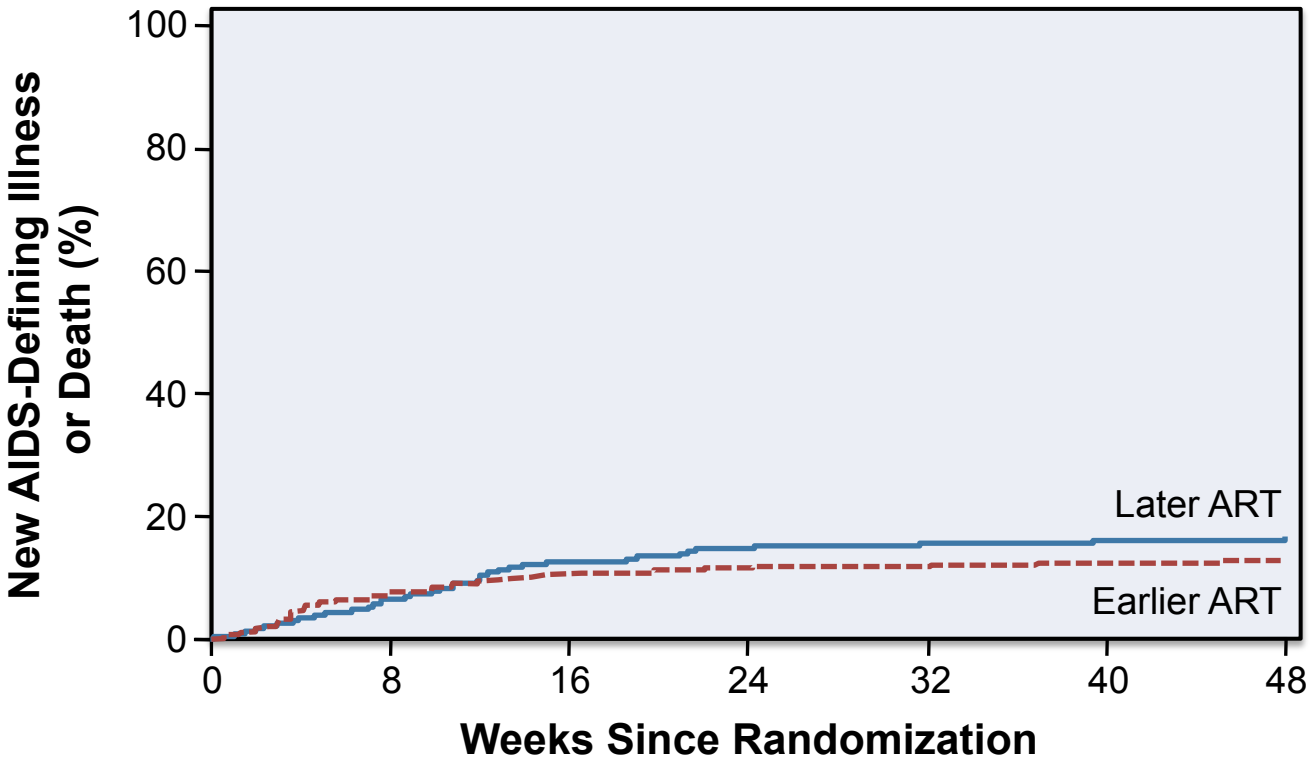
STRIDE:

- open label, randomized trial
- 806 HIV-infected patients with an absolute CD4 count less than 250 cells/mm^3 and confirmed or suspected TB
- Patients randomized to initiate antiretroviral therapy:
  - within 2 weeks after starting anti-TB therapy ("Earlier ART" arm); OR
  - 8 to 12 weeks after starting anti-TB therapy ("Later ART" arm)

Source: Diane V. Havlir, et al. N Eng J Med 2011;365:1482-91.

Figure d06a

Time to New AIDS-Defining Illness or Death

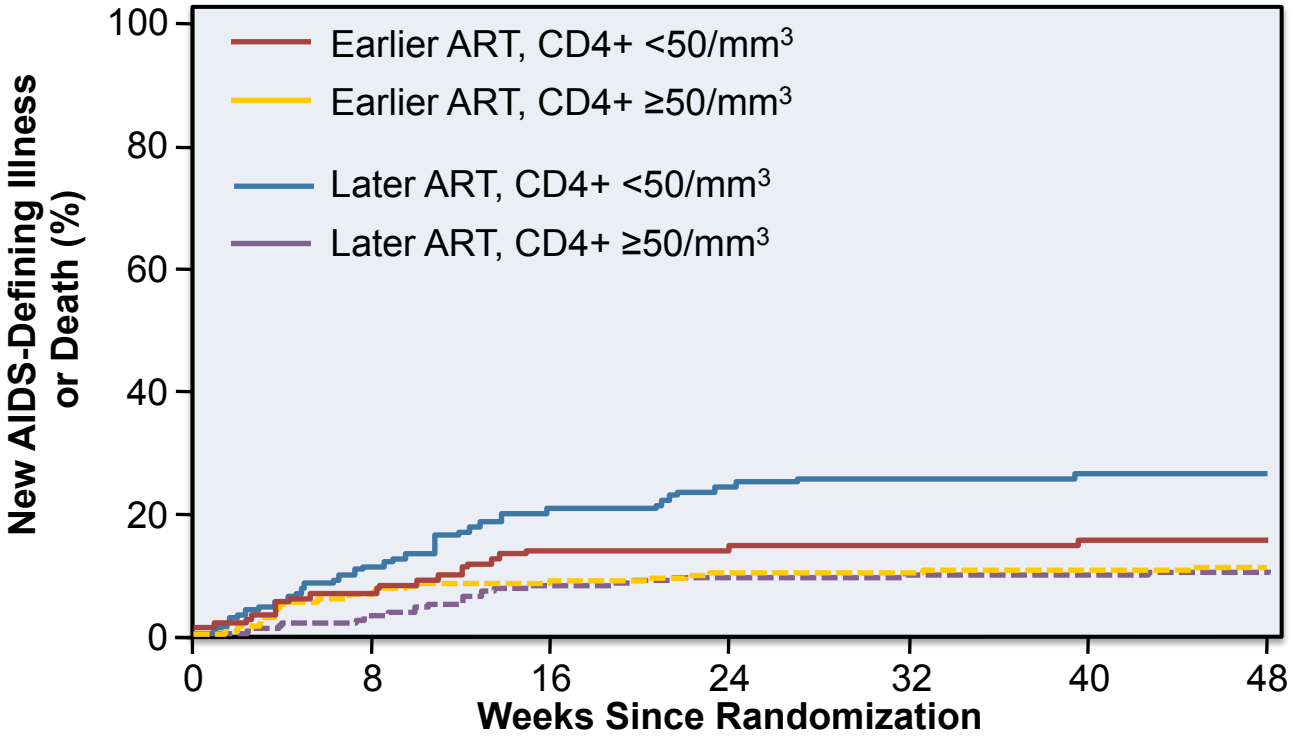


No. at Risk							
Earlier therapy	405	368	346	341	335	324	226
Later therapy	401	371	342	329	325	318	218

Source: Diane V. Havlir, et al. N Eng J Med 2011;365:1482-91.

Figure d06b

Time to New AIDS-Defining Illness or Death



No. at Risk							
Earlier therapy							
CD4+ <50/mm^3	144	132	121	121	118	114	74
CD4+ ≥50/mm^3	261	236	225	220	217	210	152
Later therapy							
CD4+ <50/mm^3	141	125	110	103	101	98	69
CD4+ ≥50/mm^3	260	246	232	226	224	220	149

Source: Diane V. Havlir, et al. N Eng J Med 2011;365:1482-91.

Case: 40 yo man with AIDS, pulmonary TB

- When should antiretroviral therapy for HIV be started for this patient?
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What about the risk of IRIS with early ART?

- Immune Reconstitution Inflammatory Syndrome (IRIS): potentially serious complication of antiretroviral therapy common in HIV/TB co-infected patients
- Higher rates of IRIS seen in early therapy arms of CAMELIA and STRIDE trials
- However, for patients with low CD4 counts, mortality was nevertheless lower for those patients in the early therapy arms, despite the higher risk of IRIS

Havlir DV, et al. N Eng J Med 2011;365:1482-91.
Blanc FX, et al. N Eng J Med. 2011;365:1471-81.

Case: 40 yo man with AIDS, pulmonary TB

- He is tolerating TB therapy: INH, rifampin, pyrazinamide, ethambutol
- He feels prepared to initiate antiretroviral therapy
- Which statement(s) is/are true concerning the initial antiretroviral therapy regimen?
  - A. Efavirenz should be avoided due to drug-drug interactions with the rifampin
  - B. Nevirapine should be avoided due to drug-drug interactions with the rifampin
  - C. Protease inhibitors should be avoided due to drug-drug interactions with the rifampin
  - D. Rifabutin will need to be substituted for rifampin before he can safely start antiretroviral therapy

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Madison Clinic Pharmacy

Tuberculosis Medication Drug Interactions

Drug	Action	Comment
Isoniazide		
PIs		
indinavir	Interaction unlikely	Isoniazide levels may be decreased by administration of indinavir but no adjustment is recommended. No data is available with boosted indinavir.
NNRTIs	Interaction unlikely	-
NRTIs		
Stavudine	Use with caution	Increased risk of peripheral neuropathy when used together
Integrase	No data	-
CCR5	No data	-
Rifampin		
PIs		
atazanavir	Contraindicated	Significantly decreases atazanavir levels
darunavir/rtv	Contraindicated	Significantly decreases darunavir levels
fosamprenavir	Contraindicated	Significantly decreases fosamprenavir levels by 82%
indinavir	Contraindicated	Significantly decreases indinavir levels by 89%
lopinavir/rtv	Contraindicated	Significantly decreases lopinavir levels by 75%
nelfinavir	Contraindicated	Significantly decreases nelfinavir levels by 82%
saquinavir/rtv	Contraindicated	Significantly decreases saquinavir levels by 84%
tipranavir/rtv	Contraindicated	Significantly decreases tipranavir levels
NNRTIs		
delavirdine	Contraindicated	Significantly decreases delaviridine levels
efavirenz	efavirenz 800 mg QD	No dose adjustment necessary for rifampin; rifampin decreases EFV by 26%
etravirine	Contraindicated	Significantly decreases etravirine levels
nevirapine	Contraindicated	Decreases nevirapine levels by 31-58%
NRTIs		
abacavir	Use with caution	Potential decrease in abacavir levels
zidovudine	Use with caution	Rifampin significantly reduces zidovudine levels
other NRTI's	Interaction unlikely	
Integrase	Raltegravir 800 mg BID Rifampin 600 mg daily	
CCR5	Maraviroc 600 mg BID	Do not use maraviroc with rifampin if efavirenz is also being used

Drug	Action	Comment
Rifabutin		
PIs		
atazanavir	Rifabutin 150 mg TIW or QOD	Information is based on atazanavir alone, no information available on boosted atazanavir, levels of atazanavir were not affected clinically
darunavir/rtv	Rifabutin 150 mg QOD	Levels of darunavir may be increased by 57% but no dose adjustment is recommended, monitor for side effects
fosamprenavir	Rifabutin 150 mg QOD	Further dose reduction may be needed
indinavir	Rifabutin 150 mg QD Indinavir 1000-1200 mg Q8h	Information based on indinavir alone
lopinavir/rtv	Rifabutin 150 mg TIW or QOD	
nelfinavir	Rifabutin 150 mg QD	No clinically significant effect on nelfinavir
saquinavir/rtv	Rifabutin 150 mg TIW	Do not use with unboosted saquinavir
tipranavir/rtv	Rifabutin 150 mg QOD	Further dose reduction may be needed, monitor for side-effects, no clinically significant effect on tipranavir
NNRTIs		
delavirdine	Contraindicated	
efavirenz	Increase rifabutin dose by 50%	Consider doubling rifabutin dose if given 2-3 times a week, no clinically significant effect on efavirenz
etravirine	See notes	Should not be given together if used with a boosted PI, if not with a boosted PI, rifabutin 300 mg QD can be used, may also decrease etravirine by 37%
nevirapine	Caution with use	Rifabutin 150 mg or 300 mg QD may be used but caution due to patient variability
NRTIs	Interaction unlikely	
Integrase	Interaction unlikely	
CCR5	No interaction in the absence of a PI	When given with tipranavir/r or fosamprenavir/r, maraviroc 300 mg BID should be used, if a different PI is used, maraviroc 150 mg BID should be used
Ethambutol		
PIs	Interaction unlikely	-
NNRTIs	Interaction unlikely	-
NRTIs	No data	-
Integrase	No data	-
CCR5	No data	-
Pyrazinamide		
PIs	Interaction unlikely	-
NNRTIs	Interaction unlikely	-
NRTIs	No data	-
Integrase	No data	-
CCR5	No data	-

WHO Recommended Antiretroviral Regimens for Persons Co-Infected with HIV and TB	
Regimen	**Comment**
Preferred Regimens	
Zidovudine + (Lamivudine or Emtricitabine) + Efavirenz *or* Tenofovir + (Lamivudine or Emtricitabine) + Efavirenz	Efavirenz dosing should not be altered since drug-drug interactions between efavirenz and rifampicin are not substantial enough to require replacement or dose-adjustment of either medication
Alternative Regimens (if efavirenz contraindicated)	
Zidovudine+ (Lamivudine or Emtricitabine) + Nevirapine *or* Tenofovir + (Lamivudine or Emtricitabine) + Nevirapine	Typical nevirapine 14-day lead-in dosing is not required in the presence of rifampicin; dosing is 200 mg twice daily throughout
Zidovudine+ (Lamivudine or Emtricitabine) + Abacavir *or* Zidovudine+ (Lamivudine or Emtricitabine) + Tenofovir	Not as potent as traditional NNRTI- or PI-based regimens, but avoids problematic drug-drug interactions
2 NRTIs + Ritonavir + Protease Inhibitor	If ritonavir-boosted PI regimen used, substitute rifabutin for rifampicin, if possible, to reduce drug-drug interactions IF PI-based therapy ***must*** be used and rifabutin not available, options include: Ritonavir/Lopinavir: 400mg/400mg twice daily *or* Ritonavir/Lopinavir: 200mg/800mg twice daily *or* Ritonavir + Saquinavir: 400mg/400mg twice daily For patients receiving rifampin and ritonavir-boosted protease inhibitor, options listed are associated with high rates of drug toxicity and therefore require close clinical and laboratory monitoring

Source: WHO, 2010; www.hivwebstudy.org