第18回日本エイズ学会

Interactive Session

症例から学ぶ HIV感染症診療のコツ

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HIV-1 and Tuberculosis Co-Infection

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Case 1

- 29 y.o. woman with a history of IDU
  - Presented to the clinic in February of 2004 with a 6 week h/o fevers, night sweats, productive cough, weight loss of ~20 lbs, and mid-thoracic back pain
  - CXR – Infiltrates in both upper and middle lung fields, RLL effusion
  - Exam – Fever 39^{o}C, tachypnea, rales both lung fields
  - Sputum AFB smear (+)
  - Spine XR demonstrated vertebral destruction at T10 level; nuclear medicine scan shows increased uptake suggesting infection/inflammatory bone involvement

Case 1

- She is found also to be HIV-seropositive
- Her initial CD4+ T cell count was 123 cells/μL and plasma HIV-1 RNA level 207,802 copies/ml
- Hgb 9.0 g/dL, WBC 25,000
- Other diagnostic evaluation is normal

Case 1

- **What would you do next?**

①Start TB treatment immediately and defer antiretroviral therapy for 2 months

②Start TB treatment immediately and defer antiretroviral therapy until completion of TB treatment

③Start both TB treatment and antiretroviral therapy now

④Do something else

Case 1

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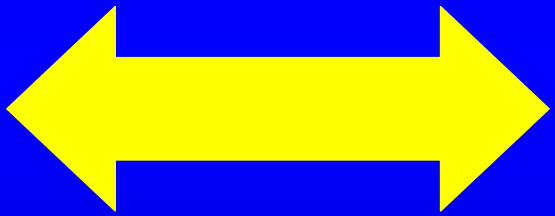
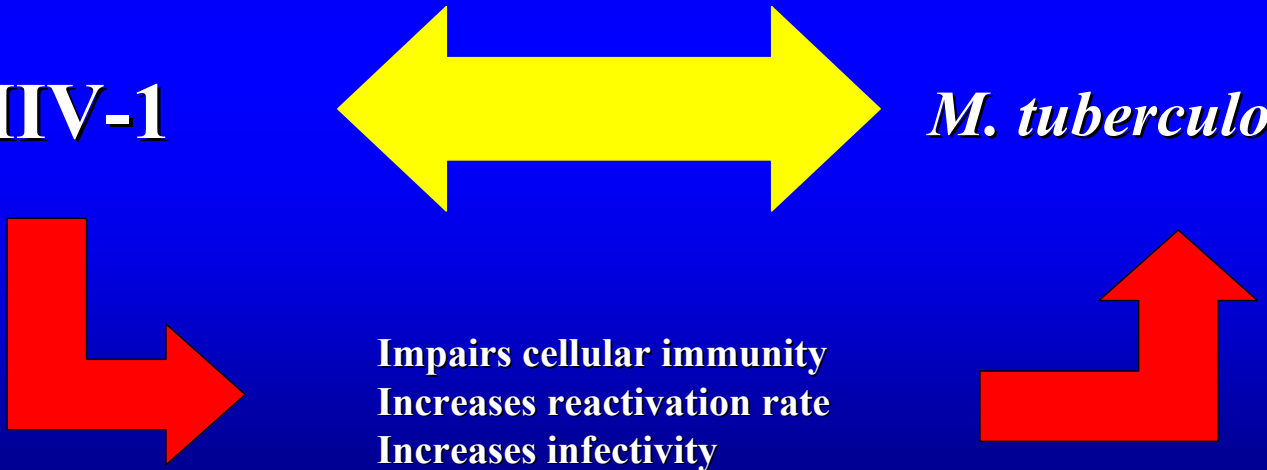
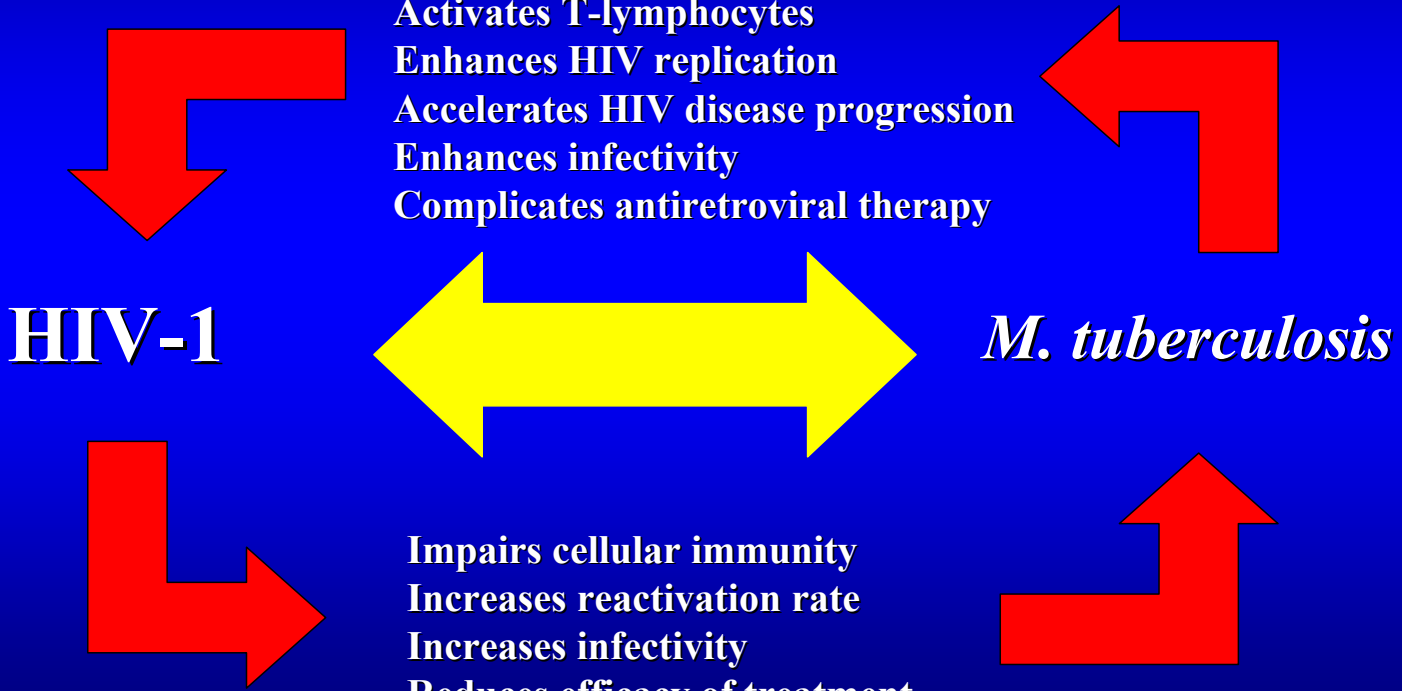
Tuberculosis-HIV Interactions

HIV-1  ***M. tuberculosis***

Tuberculosis-HIV Interactions



Tuberculosis-HIV Interactions



Natural History

- HIV increases the lifetime risk of active tuberculosis among those latently infected with TB
- Lifetime risk for TB disease in HIV seronegative individuals: 10-20%
- Yearly risk in HIV-infected persons: 7-10%

Potent ART Decreases the Risk of Developing Active Tuberculosis

- Prospective, observational study 1995-1998
  - 1360 subjects; 18 cases of TB (0.79/100 pt yrs)
  - (+) tuberculin skin test (TST) and low CD4+ T cell count were independently associated with increased risk of TB
- After controlling for TST and CD4+ T cell count:
  - RH for TB 0.09 (91% ↓) for HAART vs. no Rx or monotherapy
  - RH for TB 0.18 (82% ↓) for HAART vs. dual ARV Rx

Girardi E, et al. AIDS 2000

Issues in the Timing of Initiation of ART in Persons with Tuberculosis

- Simultaneous initiation of therapy for TB and ART:
- Potential benefits: Provides immunological improvement that may enhance the ability to successfully treat TB, and reduce early morbidity and mortality related to TB
- Potential risks: Drug interactions; immune reconstitution syndromes

Issues in the Timing of Initiation of ART in Persons with Tuberculosis

- Sequential therapy: Treatment of TB first followed by initiation of antiretroviral therapy
- Potential benefits: Avoids issues with drug interactions
- Potential risks: TB-related mortality in co-infected persons is higher in the first 3 months of therapy than in HIV-seronegative individuals, particularly if immunosuppression is severe.

Issues in the Timing of Initiation of ART in Persons with Tuberculosis

- **WHO Recommendations:**
  - < 50 CD4+ T cells/μL: Start ART and anti-TB treatment simultaneously (as soon as TB treatment is tolerated)
  - 50 – 200 CD4+ T cells/μL: Delay ART until 2 months after TB treatment is started
  - > 200 CD4+ cells/μL: Delay ART until after TB treatment is completed
- **ATS/CDC/IDSA:**
  - < 350 CD4+ T cells/μL: Individualize ART initiation; preferable to start TB therapy first, and wait 4 – 8 weeks if possible before starting ART

Management of Acute OIs in the Setting of Potent ART-CDC/NIH/IDSA Guidelines

- Cryptosporidiosis, microsporidiosis, PML, Kaposi's sarcoma
  - ART should be started immediately - No or minimally effective treatment; benefits of ART outweigh risk of ART toxicities
- TB, MAC, CMV, cryptococcal meningitis
  - Delay until there is a clinical response to OI treatment

Case 1

- The decision was made to start anti-TB and ART simultaneously because:
  - Symptoms and findings suggested disseminated TB disease
  - CD4+ T cell count was 123 cells/μL and her viral load was very high
- The patient was started on isoniazid, rifabutin, ethambutol, and pyrazinamide

Case 1

- **What antiretroviral therapy would you choose?**

①Start nevirapine, zidovudine, and lamivudine

②Start lopinavir/ritonavir (Kaletra), zidovudine and lamivudine

③Start efavirenz, zidovudine, and lamivudine

④Start ritonavir/saquinavir, zidovudine, and lamivudine

Case 1

- **What antiretroviral therapy would you choose?**

①Start nevirapine, zidovudine, and lamivudine

②Start lopinavir/ritonavir (Kaletra), zidovudine and lamivudine

③Start efavirenz, zidovudine, and lamivudine

④Start ritonavir/saquinavir, zidovudine, and lamivudine

Appropriate ART Regimens for Persons on Anti-TB Therapy

- Rifamycins are key components of successful TB treatment, therefore, ART regimens that allow continued use of a rifamycin are preferred.
- Options:

Anti-TB Regimen	ART Regimen
Rifampin-containing	Efavirenz 800 mg/d + 2 NRTIs
Rifabutin-containing*	Efavirenz 600 mg/d + 2 NRTIs
	Select PIs* + 2 NRTIs

*Rifabutin and PI doses must be adjusted

Efavirenz-Based Regimens and Rifampin in the Treatment of TB

- PK study in 24 patients with HIV and TB (Lopez-Cortez LF, et al. *Clin Pharmacokinetics* 2004)
  - Group A: Anti-TB Rx without RFP and either EFV 600 or 800 mg/d + 2 NRTIs days 1-7; RFP added day 8-14
  - Group B: Anti-TB Rx with RFP days 1-7; EFV 800 mg/d + 2 NRTIs added day 8-14

	Peak	Trough	AUC
EFV* (mean)	-24%	-25%	-22%

*Changes similar for 600 and 800 mg EFV doses

Treatment of TB with Rifampin + Efavirenz-Based Regimens

- Pilot study of 20 patients with pulmonary TB treated with ddI, 3TC, and EFV 600 mg/d plus standard TB therapy with rifampin administered simultaneously (Jack C, et al., JAIDS 2004)
  - 17/20 completed combined standard TB therapy and ART
  - TB was cured in 17/19 (89%) patients with drug-susceptible TB and 17/20 (85%) enrolled patients
  - 15/17 (88%) who completed TB therapy and ART achieved VL < 50 copies/ml and CD4+ T cell increase of 148 cells/μL

Dose Adjustments for Concomitant Use of ARV Drugs and Rifabutin

Drug	Adj ARV Dose	Adj RBT Dose*
Indinavir	1000 mg Q8h	150 mg QD
Nelfinavir	1250 mg BID	150 mg QD
Amprenavir	1200 mg BID	150 mg QD
Ritonavir (full dose)	400-600 mg BID	150 mg 2x/wk
Ritonavir (low dose)	100-200 mg BID	150 mg 2x/wk
Lopinavir/r	No adjustment	150 mg 2x/wk
Saquinavir sgc	No adjustment	300 mg QD
Efavirenz	No adjustment	450-600 mg/d
Nevirapine	No adjustment	300 mg QD

*Do not use with DLV, SQV hgc

Case 1

- After 2 months of 4-drug anti-TB treatment, her fever, infiltrates and pleural effusion resolved, and her back pain improved.
- A repeat sputum sample is AFB smear negative.
- What would you do next?

Case 1

- **What would you recommend now?**

①Switch therapy to isonizid and rifabutin twice weekly with DOT and continue treatment for 9 months

②Switch therapy to isoniazid and rifabutin twice weekly with DOT and continue treatment for 6 months

③Switch therapy to isoniazid and rifabutin daily with DOT and continue treatment for 9 months

④Continue all four anti-TB drugs for 6 months

Case 1

- **What would you recommend now?**

①Switch therapy to isonizid and rifabutin twice weekly with DOT and continue treatment for 9 months

②Switch therapy to isoniazid and rifabutin twice weekly with DOT and continue treatment for 6 months

③Switch therapy to isoniazid and rifabutin daily with DOT and continue treatment for 9 months

④Continue all four anti-TB drugs for 6 months

Treatment of HIV-1-Infected Persons with Active Pulmonary Tuberculosis

- The overall approach is similar to that in HIV-1 uninfected individuals
- Initial recommended regimen (uncomplicated pulmonary tuberculosis) for drug-susceptible TB:

INH EMB PZA RFP	INH RFP
2 months	**4 months**

Antituberculous Therapy Variations Based on Disease Characteristics

Bone or Joint Disease

INH EMB PZA RFP
2 months

INH RFP
4 months

Antituberculous Therapy Variations Based on Disease Characteristics

Bone or Joint Disease

INH EMB PZA RFP
2 months

INH RFP
4 months

Extend 3 months

Treatment Issues Unique to HIV-1-Infected Individuals CD4＜100

- Relapses are more frequent in HIV-seropositive individuals when treated with intermittent rifamycin-based regimens.
- Therefore:
  - Once weekly INH-rifapentine should not be used.
  - Twice weekly INH-rifampin or INH-rifabutin should not be used with CD4+ T cell count < 100/μL

Conclusion

- She is started on efavirenz, zidovudine and lamivudine
- Her TB treatment is successful and is discontinued after 9 months of treatment.
- Her latest CD4+ T cell count is 400 cells/μL, and her viral load is < 50 copies/ml.

When to Start Therapy and Initial Regimens

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Case 2

- 35 y.o. woman presents to her MD with a one week h/o of fevers to 39°C, headache, cough, sore throat, myalgias, generalized maculopapular skin rash, and severe fatigue.
  - Throat culture and monospot (-)
  - 5-d course of azithromycin is prescribed → no response
- Recent Medical History
  - Husband HIV(+) x 10 years
  - Reports 100% condom use/no failed condom events
  - Previously tested for HIV one year earlier and seronegative

Case 2

- She is a non-smoker, no ETOH or IDU, otherwise healthy
- PPD(-), CXR normal, WBC 3.7, ANC 1.2; LFTs normal
- Husband on ART with Kaletra®, Combivir® x 2 yrs
  - He was previously treated with nelfinavir, nevirapine, d4T, ddI, and virologically failed due to poor adherence
  - His viral load was most recently 4,950 copies/ml, CD4+ 357 cells/μL
  - He was treated for acute gonorrhea in 11/01
- HIV EIA is positive, Western Blot indeterminate

Case 2

- CD4+ T cell count 525 cells/μL
- Plasma HIV-1 RNA level 136,000 copies/ml
- Clinical symptoms gradually resolve over 14 days
- She wishes to explore enrollment in a clinical trial for treatment of acute HIV infection

Case 2

- **What would you recommend next?**

①Proceed with a randomized clinical trial

②Treat her immediately with antiretroviral therapy outside of a clinical trial

③Do a resistance test

④Defer treatment and observe

Case 2

- **What would you recommend next?**

①Proceed with a randomized clinical trial

②Treat her immediately with antiretroviral therapy outside of a clinical trial

③Do a resistance test

④Defer treatment and observe

Case 2

- A genotypic resistance test is performed on her virus with the following results:
- NRTI mutations – M184V, R211K, K219N
- NNRTI mutations – K103N, Y181C
- PI mutations – L10I, L63P, V77I, L90M

Case 2

- Based on these data, she decided to enroll in the "no treatment" arm of the planned clinical trial

Date	CD4+ Count	HIV-1 RNA
May 2003	525 (25%)	136,000 c/ml
July 2003	483 (29%)	26,487 c/ml
Sept 2003	410 (28%)	197,210 c/ml
Nov 2003	378 (26%)	112,400 c/ml
Jan 2004	330 (20%)	55,299 c/ml

Case 2

- What would you recommend now?

①Start ART now

②Delay ART until CD4+ T cell count < 200 cells/μL

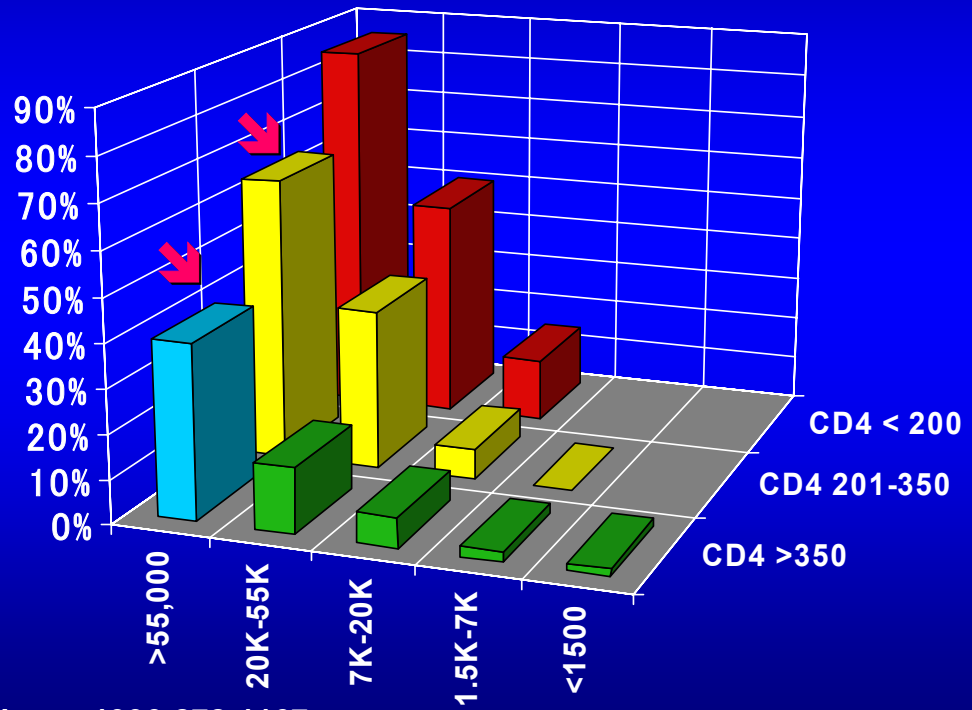
③Delay ART until plasma HIV-1 RNA level > 100,000 copies/ml

④None of the above

When To Start Antiretroviral Therapy

- Current dilemma – Weighing the potential benefits with the potential risks of ART for:
  - Asymptomatic persons with CD4+ counts between 200 - 500 cells/μL
    - Low to moderate risk of disease progression
    - Low to moderate risk of complications of therapy

Risk of Progression to AIDS in 3 Years by Baseline CD4+ Count and HIV-1 RNA



Mellors et al, Science 1996;272:1167

Benefits and Potential Risks of Earlier Therapy (DHHS 2004 Guidelines)

Benefits

- Control of viral replication easier to achieve/maintain
- Delay or prevention of immunodeficiency
- Lower risk of resistance
- Decreased risk of HIV transmission

Risks

- Drug-related reduction in quality of life
- Greater cumulative drug-related adverse events
- Development of drug resistance in those with poor adherence
- Limitation of future treatment options

Rationale for Later Initiation of Therapy

- Complications of ART may have short and long-term effects on future health
  - Pancreatitis
  - Lactic acidosis/mitochondrial dysfunction
  - Hepatotoxicity
  - Hyperlipidemia
    - Increase risk of cardiovascular disease
  - Body fat abnormalities/lipoatrophy
  - Hyperglycemia
  - Peripheral neuropathy
  - Osteopenia/osteoporosis

CD4 + Count is Better than Plasma HIV-1 RNA in Determining When to Initiate ART

- Retrospective review – risk of new OI or death (N=1173)
- Median durations of ART and F/U – 29 and 36 mos
- Among pts who achieved sustained virologic suppression, ART started with:
  - CD4+ of counts 201-350 cells/μL
    - Statistically significant delay in disease progression compared to CD4+ < 200 cells/μL (P<0.0001; 0.09)
  - CD4+ counts of 201-350 cells/μL
    - No difference in disease progression compared to CD4+ > 350 cells/μL (P=0.38; 0.40)
- But, lower CD4+ count at onset of ART - significantly less likely to achieve sustained virologic suppression

T Sterling et al, JID 2003; 188:1659-65

Later Initiation of Antiretroviral Therapy is Associated with Increased Risk of Death

- CDC Adult Spectrum of Disease Project; record review of 2,729 persons starting ART 1996-2002 evaluating CD4+ at time of starting ART

CD4+	# OIs	Deaths	HR (95% CI)
0 – 49	77	19	6.3 (4.0, 10.0)
50 – 199	76	33	3.5 (2.2, 5.4)
200 – 349	34	23	1.7 (1.1, 2.7)
350 – 499	24	11	1.5 (0.9, 2.5)
≥ 500	17	10	Referent
Overall	228	96	----------

- Conclusion: ART should not be deferred until the CD4+ cell count reaches < 200 cells/μL

JE Kaplan et al, CID 2003; 37

Indications for Initiation of Antiretroviral Therapy - DHHS 2004 Guidelines

Clinical Category	CD4 Count	HIV RNA	Recommendation
Symptomatic	Any	Any	Treat
Asymptomatic	< 200	Any	Treat
Asymptomatic	200-350	Any	Offer treatment
Asymptomatic	> 350	> 55,000	Offer or defer
Asymptomatic	> 350	< 55,000	Generally defer

Case 2

- What would you recommend?

①Start ART now

②Delay ART until CD4+ T cell count < 200 cells/μL

③Delay ART until plasma HIV-1 RNA level > 100,000 copies/ml

④None of the above

Case 2

- What regimen would you start?
- (NRTI mutations M184V, R211K, K219N; NNRTI mutations K103N, Y181C; PI mutations L10I, L63P, V77I, L90M)
  - ①Fixed dose zidovudine/lamivudine/abacavir (Trizivir®) plus lopinavir/ritonavir (Kaletra®)
  - ②Fixed dose zidovudine/lamivudine (Combivir®) + efavirenz
  - ③Tenofovir + Combivir® + Kaletra®
  - ④Tenofovir + didanosine + atazanavir/ritonavir
  - ⑤Other

Persistence of Transmitted Drug Resistance

- 11 persons with primary HIV-1 infection who deferred ART
  (Little S, et al., 11th CROI, 2004; Abstr. 36LB)
  - Mean time from date of infection was 65 days
  - Longitudinal samples collected for a median of 225 days (range 82-1346) after infection
  - 7 pts had NNRTI, 2 had NRTI + PI, 1 had NNRTI + PI, and 1 had 3-class resistance mutations
  - Complete shift to wild type virus in peripheral blood occurred in only one patient 1019 days after infection
  - For those with PI mutations, no shift to WT virus at PI loci was observed up to 342 days after infection

Case 2

- What regimen would you start?
- (NRTI mutations M184V, R211K, K219N; NNRTI mutations K103N, Y181C; PI mutations L10I, L63P, V77I, L90M)
  - ①Fixed dose zidovudine/lamivudine/abacavir (Trizivir®) plus lopinavir/ritonavir (Kaletra®)
  - ②Fixed dose zidovudine/lamivudine (Combivir®) + efavirenz
  - ③Tenofovir + Combivir® + (Kaletra®)
  - ④Tenofovir + didanosine + atazanavir/ritonavir
  - ⑤Other

Recommended Antiretroviral Regimens for Treatment-Naïve Persons

Preferred

- EFV* + 3TC + (ZDV or TDF or d4T)
- LPV/r + 3TC + (ZDV or d4T)

*EFV should be avoided in pregnant women

**Only when preferred or other alternative regimen cannot be used

Alternative

- NNRTI-Based
  - EFV* + FTC + (ZDV or TDF or d4T)
  - EFV* + (3TC or FTC) + (ddI or ABC)
  - NVP + (3TC or FTC) + (ZDV or d4T or ddI or ABC)
- Triple NRTI-Based
  - ABC + 3TC + (ZDV or d4T)**

DHHS Guidelines, March 23, 2004; www.aidsinfo.nih.gov

Recommended Antiretroviral Regimens for Treatment-Naïve Persons

Alternative regimens (cont'd)

- PI-Based
  - ATZ + (3TC or FTC) + (ZDV or d4T or ABC)
  - FosAPV + (3TC or FTC) + (ZDV or d4T or ABC)
  - FosAPV/RTV + (3TC or FTC) + (ZDV or d4T or ABC)
  - IDV/RTV + (3TC or FTC) + (ZDV or d4T or ABC)
  - LPV/RTV + FTC + (ZDV or d4T or ABC)
  - LPV/RTV + 3TC + ABC
  - NFV + (3TC or FTC) + (ZDV or d4T or ABC)
  - SQV/RTV + (3TC or FTC) + (ZDV or d4T or ABC)

DHHS Guidelines, March 23, 2004; www.aidsinfo.nih.gov

When Should ART be Started and With What Regimen?

- No single answer is valid for every patient
- Factors to consider:
  - Biological factors
    - CD4+ T cell count
    - Plasma HIV-1 RNA level
    - Toxicities and risk factors for their development
    - Transmitted drug resistance
  - Commitment to therapy
    - Social and demographic factors, ability to adhere
- **Flexibility and individualization**

HIV-1 and HBV Co-Infection

Case 3

- 43 year old injecting drug user first found to be HIV-1 seropositive in 1995
- Lost to medical follow-up
- Clinically well through 2003 when he went to his physician with fatigue and weight loss
- Found to have a CD4 cell count of 86 cells/mm^3

Initial Evaluation

- PPD-
- CXR normal
- HCV Ab-
- HBSAg+
- HBV DNA level: 730,000 copies/ml
- LFT's: ALT, AST both 1.5 times upper limit of normal (ULN).

Clinical Course

- Started on AZT/3TC + efavirenz
- 8 weeks later:
  Fever, nausea, malaise, jaundice
- Evaluation:
  T: 38.7^{0}C; other vital signs normal
  Mild scleral icterus
  Liver edge 4 cm below right costal margin
- CD4 cell count: 220 cells/mm^{3}
- LFT's: 6 x ULN

What would you do?

①Obtain HAV and HCV serologies
②Stop the efavirenz
③Stop all the antiretroviral drugs
④Perform a liver biopsy
⑤Make no changes

Continued Clinical Course

- Continued on ARV's
- LFT's dropped back to 1.5x ULN
- HBV DNA 12,000 copies/ml

- 10 months later:
  HIV-1 RNA undetectable
  CD4 cell count 350 cells/mm^3
  LFT's flared with LFT's again 6x ULN
  HBV DNA level 220,000 copies/ml

What Would You Do Now?

①Stop all antiretrovirals.
②Add prednisone.
③Change AZT/3TC to TDF/3TC
④Perform a liver biopsy.

Mechanisms of 3TC-Associated Liver Flare in 3TC-Treated Patients

1). Immune reconstitution.

2). Resumption of HBV replication

   a). 3TC withdrawal

   b). Development of YMDD mutation

LFT Elevation in Patients Receiving 3TC

Case no.	Alanine aminotransferase level (U/L)	Bilirubin level (μmol/L)	HBeAg	Antibody to HBeAg
1	1,408	162.5	+	–
2	1,041	15.4	NT	NT
3	163	49.6	–	–
4	423	104.3	+	–
5	459	13.7	+	–

Bessesen, et. al., CID 1999

Approach to Managing LFT Flares in Co-Infected Patients

1). Immune reconstitution.

Observe or short course steroids

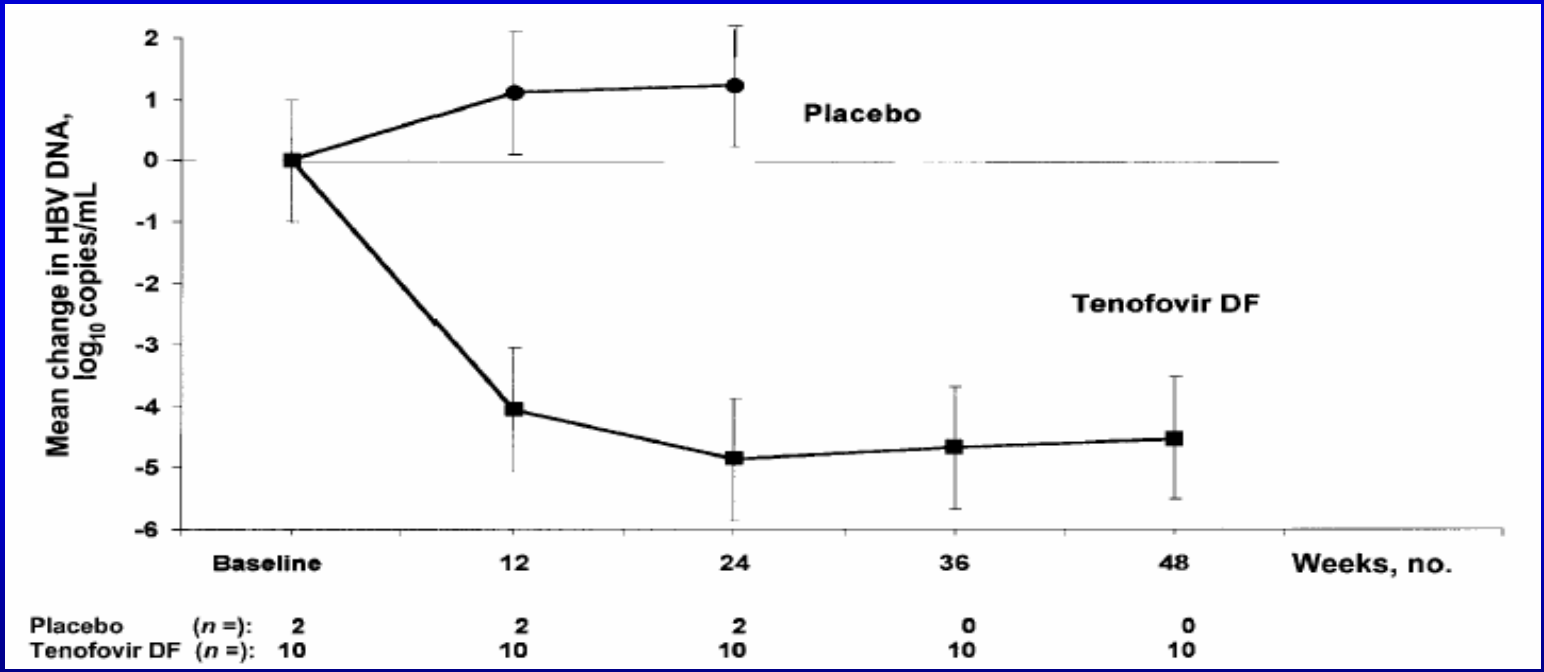
2). Resumption of HBV replication

Control HBV replication

a). Resume 3TC

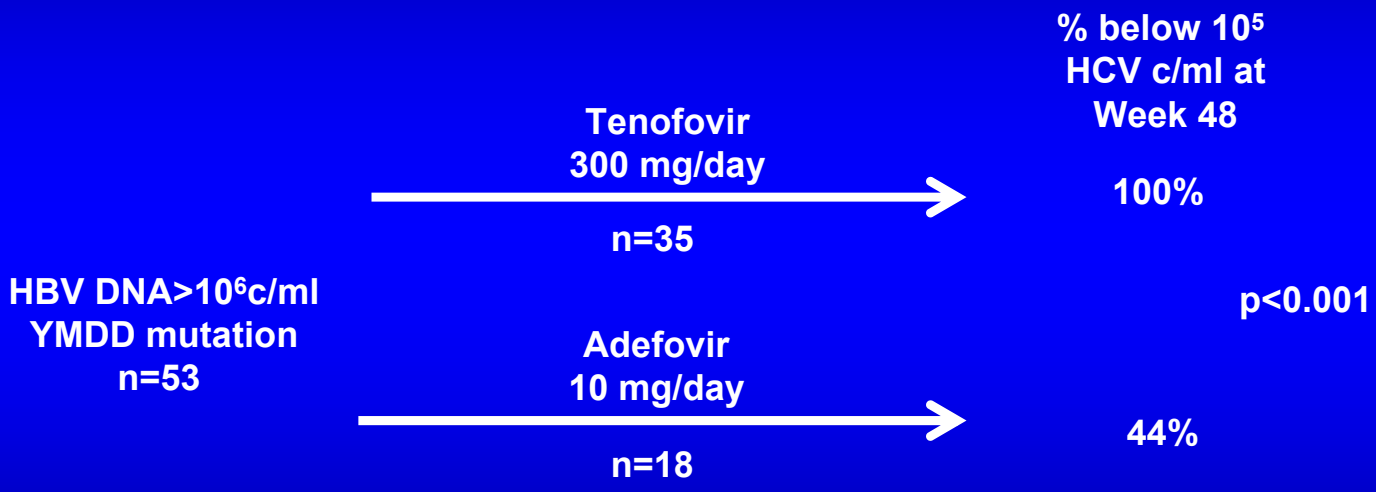
b). Development of YMDD mutation:use alternate

Response of HBV to Tenofovir in Co-Infected Patients



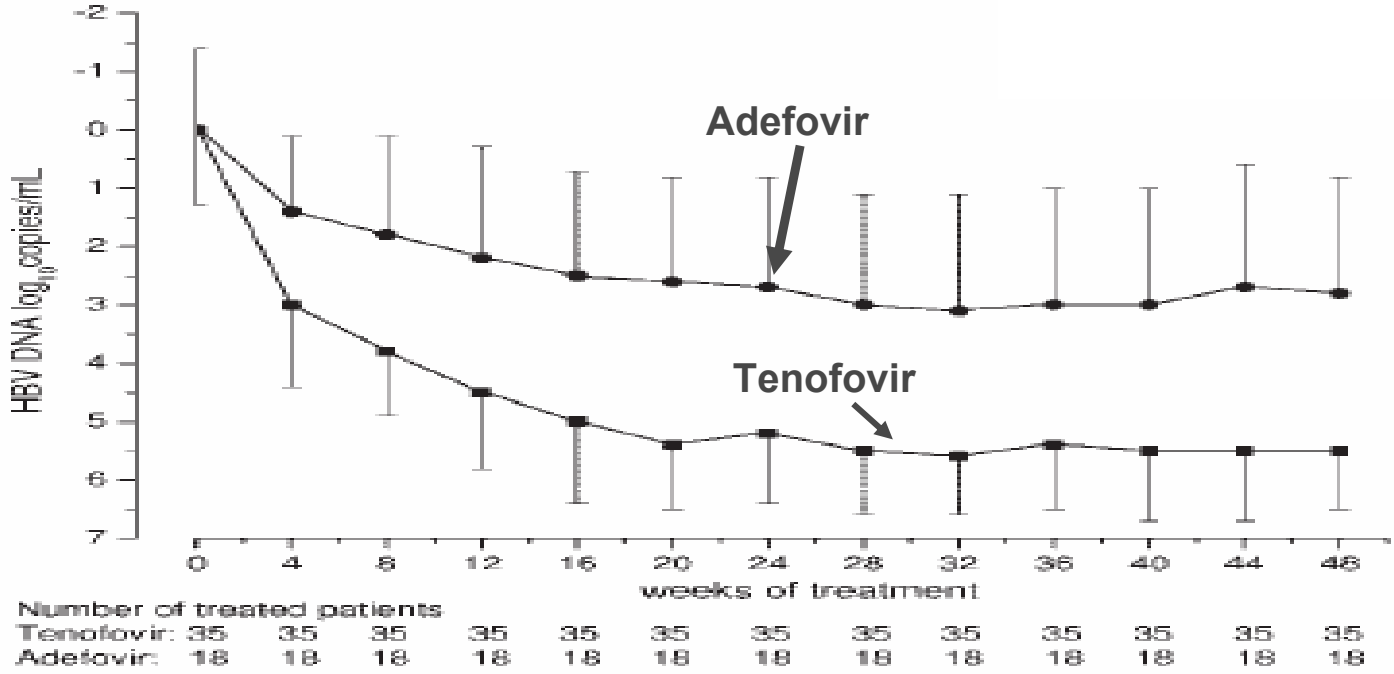
Cooper, et.al., JID 2004

Tenofovir vs. Adefovir in HBV Infection



van Bommel et. al., Hepatology 2004

Responsiveness of HBV to Tenofovir or Adefovir



HIV-1 and HCV Co-Infection

Case 4

- 47 year old hemophiliac with HIV infection first treated with AZT/3TC/indinavir in 1995 when his CD4 cell count was 190 cells/mm^3.

Clinical Course

- During initial evaluation found to be HCV Ab+

- No clinical evidence of liver disease.
- LFT's 1.3 x upper limit of normal (ULN).

Clinical Course

- 2004: Malaise, fatigue
- Physical examination: Normal abdominal exam; no evidence of liver disease
- Laboratory findings: CD4:408/mm^3LFT's 3x ULN; HCV RNA level 1,000,000 copies/ml; HCV genotype 2

What Would You Do Now?

①Biopsy his liver.
②Treat with interferon-alpha.
③Change the indinavir to efavirenz.
④Treat with PEG-Ifn/ribavirin.
⑤Observe.

Treatment of HCV with PEG-Ifn/ Ribavirin: ACTG 5071

Table 2. Rates of Virologic Response.

Virologic Response	Interferon and Ribavirin (N=67)	Peginterferon and Ribavirin (N=66)	P Value	Genotype 1 Infection		Non–Genotype 1 Infection	
				Interferon and Ribavirin (N=52)	Peginterferon and Ribavirin (N=51)	Interferon and Ribavirin (N=15)	Peginterferon and Ribavirin (N=15)
	no. (%)			*no. (%)*		*no. (%)*	
At week 24	10 (15)	29 (44)	<0.001	4 (8)	17 (33)*	6 (40)	12 (80)
At end of treatment	8 (12)	27 (41)	<0.001	3 (6)	15 (29)	5 (33)	12 (80)†
Sustained	8 (12)	18 (27)	0.03	3 (6)	7 (14)	5 (33)†	11 (73)†‡

* P=0.001 for the comparison with the group given interferon and ribavirin.
† P<0.001 for the comparison with the subjects in the same group with a genotype 1 infection.
‡ P=0.07 for the comparison with the group given interferon and ribavirin with a non–genotype 1 infection.

Chung, et. al., NEJM, 2004

Treatment of HCV with PEG-Ifn/ Ribavirin: ACTG 5071

Table 2. Rates of Virologic Response.

Virologic Response	Interferon and Ribavirin (N=67)	Peginterferon and Ribavirin (N=66)	P Value	Genotype 1 Infection		Non–Genotype 1 Infection	
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At week 24	10 (15)	29 (44)	<0.001	4 (8)	17 (33)*	6 (40)	12 (80)
At end of treatment	8 (12)	27 (41)	<0.001	3 (6)	15 (29)	5 (33)	12 (80)†
Sustained	8 (12)	18 (27)	0.03	3 (6)	7 (14)	5 (33)†	11 (73)†‡

* P=0.001 for the comparison with the group given interferon and ribavirin.
† P<0.001 for the comparison with the subjects in the same group with a genotype 1 infection.
‡ P=0.07 for the comparison with the group given interferon and ribavirin with a non–genotype 1 infection.

Chung, et. al., NEJM, 2004

Treatment of HCV in Co-Infected Patients

1). Sustained virologic responses less frequent in co-infected patients than in mono-infected patients

2). Genotype 1 patients much less responsive than those with genotypes 2 and 3

3). Optimal sequence of when to treat HCV and HIV not yet fully delineated