Update on Antiretroviral Therapy in Adults

Khuanchai Supparatpinyo
Department of Medicine
Chiang Mai University

Objectives

- When to start?
- What to start?
- ART in patients with active OI
- HIV treatment failure

When to Start?

- Exact CD4 count at which to initiate therapy is not known, but evidence points to starting at higher counts
- 2 large RCTs (START and TEMPRANO) have addressed the optimal time to initiate ART

Strategic Timing of Antiretroviral Therapy (START)

- 4685 HIV-positive adults with CD4>500 cells/mm^3 were followed for a mean of 3.0 years
- Randomized to
  - start ART immediately, or
  - defer until the CD4<350 cells/mm^3 or until the development of AIDS or condition that dictated the use of ART
- Primary composite end point:
  - serious AIDS-related event
  - serious non–AIDS-related event
  - death from any cause

The INSIGHT START Study Group. N Engl J Med 2015 Jul 20. [Epub ahead of print]

START: Primary and Secondary End Points

End Point	Immediate-Initiation Group (N = 2326)		Deferred-Initiation Group (N = 2359)		Hazard Ratio (95% CI)†	P Value
	no.	*no./100 person-yr*	*no.*	*no./100 person-yr*		
Composite primary end point	42	0.60	96	1.38	0.43 (0.30–0.62)	<0.001
Components of the primary end point						
Serious AIDS-related event	14	0.20	50	0.72	0.28 (0.15–0.50)	<0.001
Serious non–AIDS-related event	29	0.42	47	0.67	0.61 (0.38–0.97)	0.04
Death from any cause	12	0.17	21	0.30	0.58 (0.28–1.17)	0.13
Tuberculosis	6	0.09	20	0.28	0.29 (0.12–0.73)	0.008
Kaposi's sarcoma	1	0.01	11	0.16	0.09 (0.01–0.71)	0.02
Malignant lymphoma	3	0.04	10	0.14	0.30 (0.08–1.10)	0.07
Cancer not related to AIDS	9	0.13	18	0.26	0.50 (0.22–1.11)	0.09
Cardiovascular disease	12	0.17	14	0.20	0.84 (0.39–1.81)	0.65
Other secondary end points						
Grade 4 event‡	73	1.06	73	1.05	1.01 (0.73–1.39)	0.97
Unscheduled hospitalization§	262	4.02	287	4.40	0.91 (0.77–1.08)	0.28
Grade 4 event, unscheduled hospitalization, or death from any cause	283	4.36	311	4.78	0.91 (0.77–1.07)	0.25

The INSIGHT START Study Group. N Engl J Med 2015 Jul 20. [Epub ahead of print]

Conclusions

- The initiation of antiretroviral therapy in HIV-positive adults with a CD4+ count >500 cells/mm^3 provided net benefits over starting such therapy in patients after the CD4+ count had declined to 350 cells/mm^3

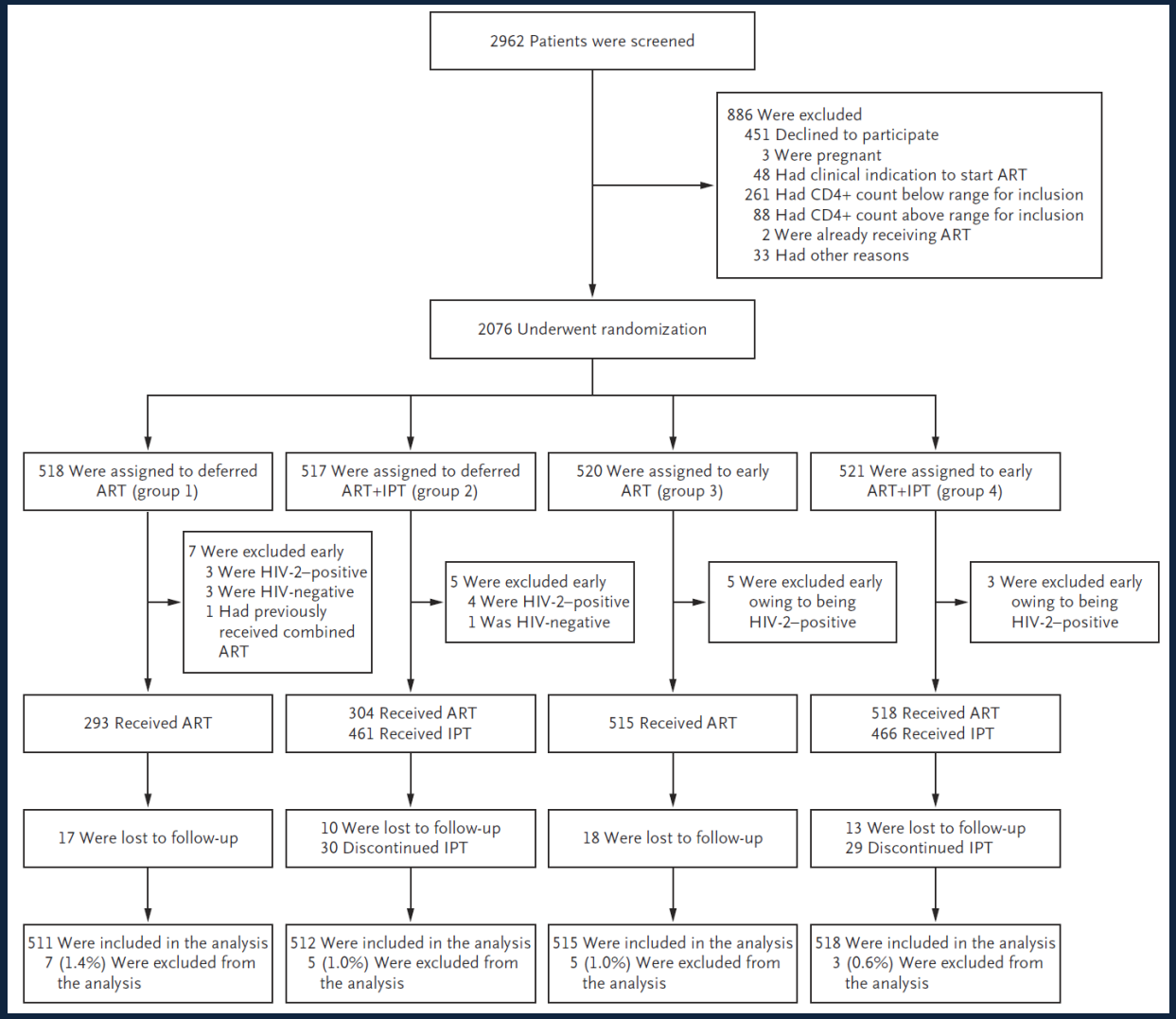
The INSIGHT START Study Group. N Engl J Med 2015 Jul 20. [Epub ahead of print]

A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa (TEMPRANO)

- CD4+ count <800 cells/mm^3 without WHO indication for ART
- Participants were randomly assigned to
  - deferred ART
  - deferred ART plus IPT
  - early ART
  - early ART plus IPT
- The primary end point was a composite of diseases or death from any cause at 30 months

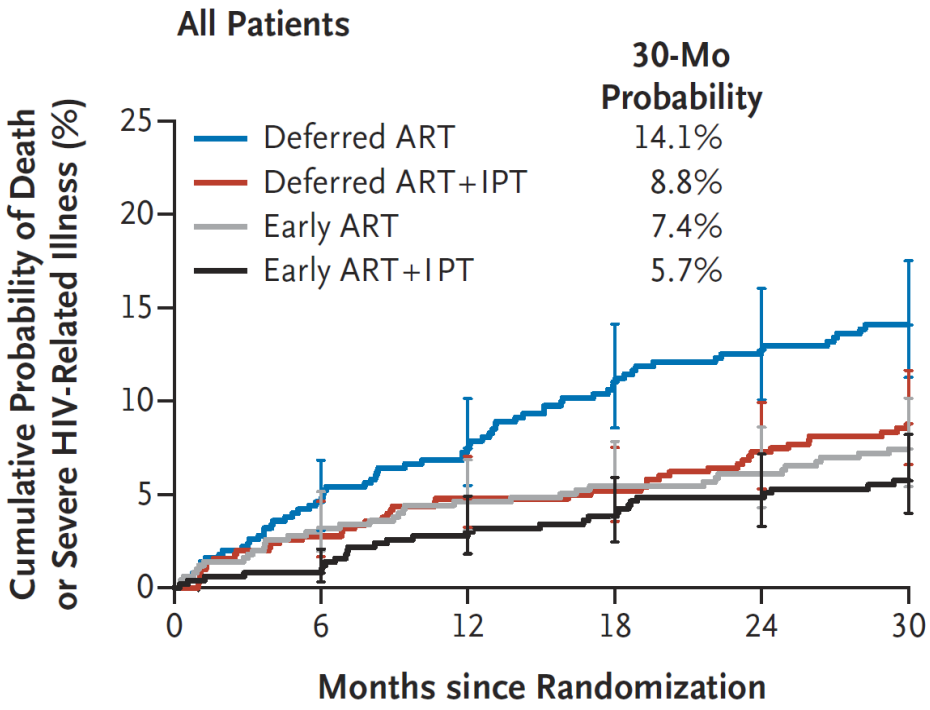
The TEMPRANO ANRS 12136 Study Group. N Engl J Med 2015;373:808-22.

TEMPRANO Study



The TEMPRANO ANRS 12136 Study Group. N Engl J Med 2015;373:808-22.

Primary outcome



No. at Risk

Deferred ART	511	473	448	418	400	366
Deferred ART+IPT	512	489	473	459	440	419
Early ART	515	481	463	452	432	403
Early ART+IPT	518	501	478	459	445	418

The risk of death or severe HIV-related illness was lower with early ART than with deferred ART

Conclusions

- In this African country, immediate ART and 6 months of IPT independently led to lower rates of severe illness than did deferred ART and no IPT, both overall and among patients with CD4+ counts ≥500 cells/mm^3

The TEMPRANO ANRS 12136 Study Group. N Engl J Med 2015;373:808-22.

When to start?

- ART is recommended for all HIV-infected individuals, regardless of CD4 T lymphocyte cell count, to reduce the morbidity and mortality associated with HIV infection **(AI)**

DHHS guidelines, January 2016

When to start?

Adults[a] (>19 years)	ART should be initiated in all adults living with HIV at any CD4 cell count	*Strong*	*Moderate* NEW
	As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cells/mm^3	*Strong*	*Moderate*
Pregnant and breastfeeding women	ART should be initiated in all pregnant and breastfeeding women living with HIV at any CD4 cell count and continued lifelong	*Strong*	*Moderate* UPDATED

WHO Recommendation, Sep 2015

When to start?

เกณฑ์การเริ่มยาต้านไวรัสในประเทศไทย

- ให้ยาต้านไวรัสในผู้ติดเชื้อทุกรายในทุกระดับ CD4 โดยเฉพาะอย่างยิ่งกรณี CD4 < 500 cells/mm^3

ในกรณี CD4 > 500 cells/mm^3 ควรพิจารณาประเด็นต่อไปนี้อย่างเคร่งครัด

- ผู้ติดเชื้อที่จะเริ่มยาต้านไวรัสต้องเข้าใจถึงประโยชน์และผลข้างเคียงของการรักษา เข้าใจประเด็นความสำคัญของ adherence ยินดีที่จะเริ่มยาต้านไวรัสและมีความมุ่งมั่นตั้งใจรับยาต้านไวรัสอย่างสม่ำเสมอ
- ผู้ติดเชื้อมีสิทธิเลือกที่จะยังไม่รับยาถ้ายังไม่พร้อมในการเริ่มยาต้านไวรัส
- ในกรณีผู้ติดเชื้อที่ยังไม่มีอาการ ประโยชน์ต่อตัวผู้ติดเชื้อเองยังไม่ชัดเจน แต่มีประโยชน์ในด้านการสาธารณสุขเพื่อลดการถ่ายทอดเชื้อ
- ผู้ให้การดูแลรักษาควรพิจารณาเลื่อนการเริ่มยาไปก่อน หากพบมีปัญหาทางสภาพจิตใจหรือสังคมที่ไม่เหมาะต่อการกินยาต่อเนื่อง

Thai Guidelines, Sep 2014

HIV Prevention

- ART is also recommended for HIV-infected individuals to prevent HIV transmission **(AI)**
- Perinatal transmission
  - use of combination ART during pregnancy has reduced the rate of perinatal transmission of HIV from approximately 20% to 30% to 0.1% to 0.5%
- Sexual transmission
  - HPTN 052 (1,763 HIV-serodiscordant couples): 96% reduction in transmission associated with early ART (HR 0.04; 95% CI, 0.01–0.27; *P*<0.001)

DHHS guidelines, January 2016

Oral pre-exposure prophylaxis to prevent HIV acquisition

HIV-negative individuals at substantial risk of HIV infection[b]	Oral PrEP (containing TDF) should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches	*Strong*	*High* NEW

WHO Recommendation, Sep 2015

What to Start?

DHHS guidelines, January 2016

Recommended Regimen Options

INSTI based (AI)	▪ DTG/ABC/3TC (HLA-B*5701 negative) ▪ DTG + TDF/FTC ▪ EVG/c/TAF/FTC (CrCl≥30) ▪ EVG/c/TDF/FTC (CrCl≥70) ▪ RAL + TDF/FTC
PI based (AI)	▪ DRV/r + TDF/FTC

DHHS guidelines, January 2016

Alternative Regimen Options

NNRTI based	▪ EFV/TDF/FTC (BI) ▪ RPV/TDF/FTC (VL<100000, BI)
PI based	▪ ATV/c + TDF/FTC (CrCl ≥70 mL/min, BI) ▪ ATV/r + TDF/FTC (BI) ▪ (DRV/c or DRV/r) + ABC/3TC (BIII and BII) ▪ DRV/c + TDF/FTC (CrCl ≥70 mL/min, BII)

DHHS guidelines, January 2016

Other Regimen Options

INSTI based	▪ RAL + ABC/3TC (CII)
NNRTI based	▪ EFV + ABC/3TC (VL<100000, CI)
PI based	▪ (ATV/c or ATV/r) + ABC/3TC[1,2] (CIII, CI) ▪ LPV/r (QD or BID) + ABC/3TC (CI) ▪ LPV/r (QD or BID) + TDF/FTC (CI)
Other	▪ DRV/r + RAL (VL<100000, CD4>200, CI) ▪ LPV/r (BID) + 3TC (CI)

DHHS guidelines, January 2016

First-line ART regimens for adults

First-line ART for adults (including pregnant and breastfeeding women and people with TB and HBV coinfection)	
Preferred regimens	TDF + 3TC (or FTC) + EFV
Alternative regimens	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + NVP
Special circumstances[c]	Regimens containing ABC, d4T[b] and boosted PIs

WHO Recommendation, Jun 2013

First-line ART regimens for adults

NRTI backbone		NNRTIs		ยาตัวที่สามอื่น ๆ
แนะนำ		แนะนำ		แนะนำ
TDF/FTC		EFV	→ ในกรณีที่ผู้ป่วยไม่สามารถกินยา NNRTIs ได้	LPV/r
TDF + 3TC*	+			
หรือทางเลือก		หรือ		หรือ
ABC + 3TC AZT + 3TC		RPV NVP		ATV/r

Thai Guidelines, Sep 2014

ART in patients with active OI

Considerations

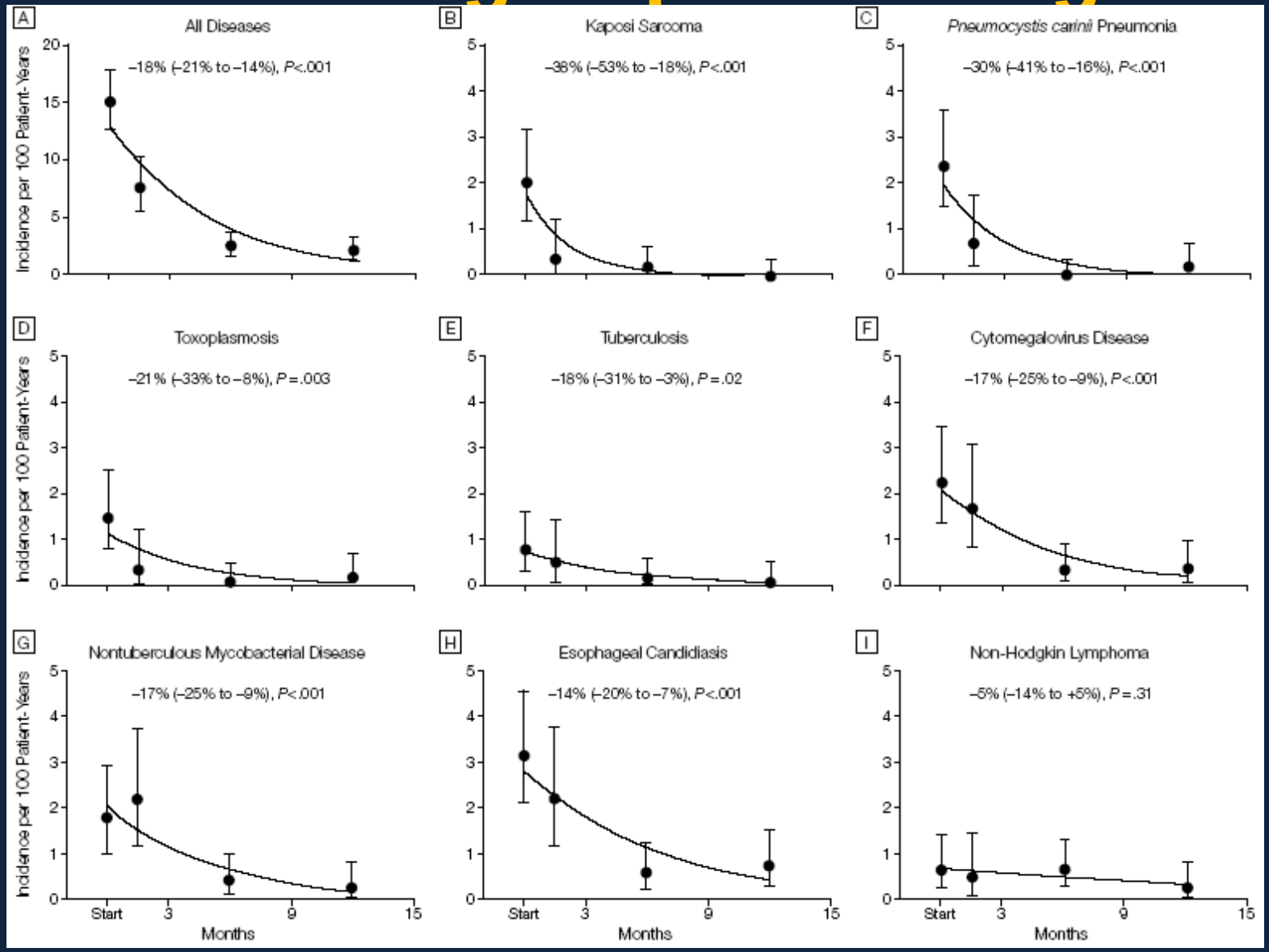
- Degree of immunosuppression
- Availability of effective therapy for the OI
- Risk of drug interactions
- Overlapping drug toxicities
- Risk of the consequences of the development of IRIS
- Willingness of the patient to adhere to drug regimens

NIH, CDC, HIVMA/IDSA Guidelines for prevention and treatment of OI, June 2008

Worsening of patients after initiation of ART

- **ARV adverse effects/complications**
- **Breakthrough of OI or inflammatory reactions after ART**
  - Unmasking of preexisting OI
  - Immune reconstitution inflammatory syndrome (IRIS)
  - Recurrence of OI due to antiretroviral failure

Unmasking of preexisting OI



OIs occurring after initiation of HAART

- Retrospective observational study in 2154 HIV patients (ACTG trials)
- OI occurred in fewer than 20% of patients on HAART
  - Major OIs: 5%, Minor OIs: 17%
- Approximately half occurred after first 6 months of HAART

Smurzynski M, et al. J Acquir Immune Defic Syndr. 2010 Sep 1;55(1):117-27.

OIs occurring after initiation of HAART

- Risk factors for development of OIs
  - History of OIs
  - Low baseline CD4+ cell count*
  - High baseline plasma HIV-1 RNA level*
  - Female sex
  - Older age

*Risk factors for OIs in early months of HAART

Smurzynski M, et al. J Acquir Immune Defic Syndr. 2010 Sep 1;55(1):117-27.

Immune Reconstitution Inflammatory Syndrome (IRIS)

- AIDS patient
- Receiving ART with increased CD4 cells and suppressed plasma viral load
- Symptoms/signs compatible with OI or inflammatory reactions after ART
- Symptoms/signs are not due to new OI and adverse drug reactions

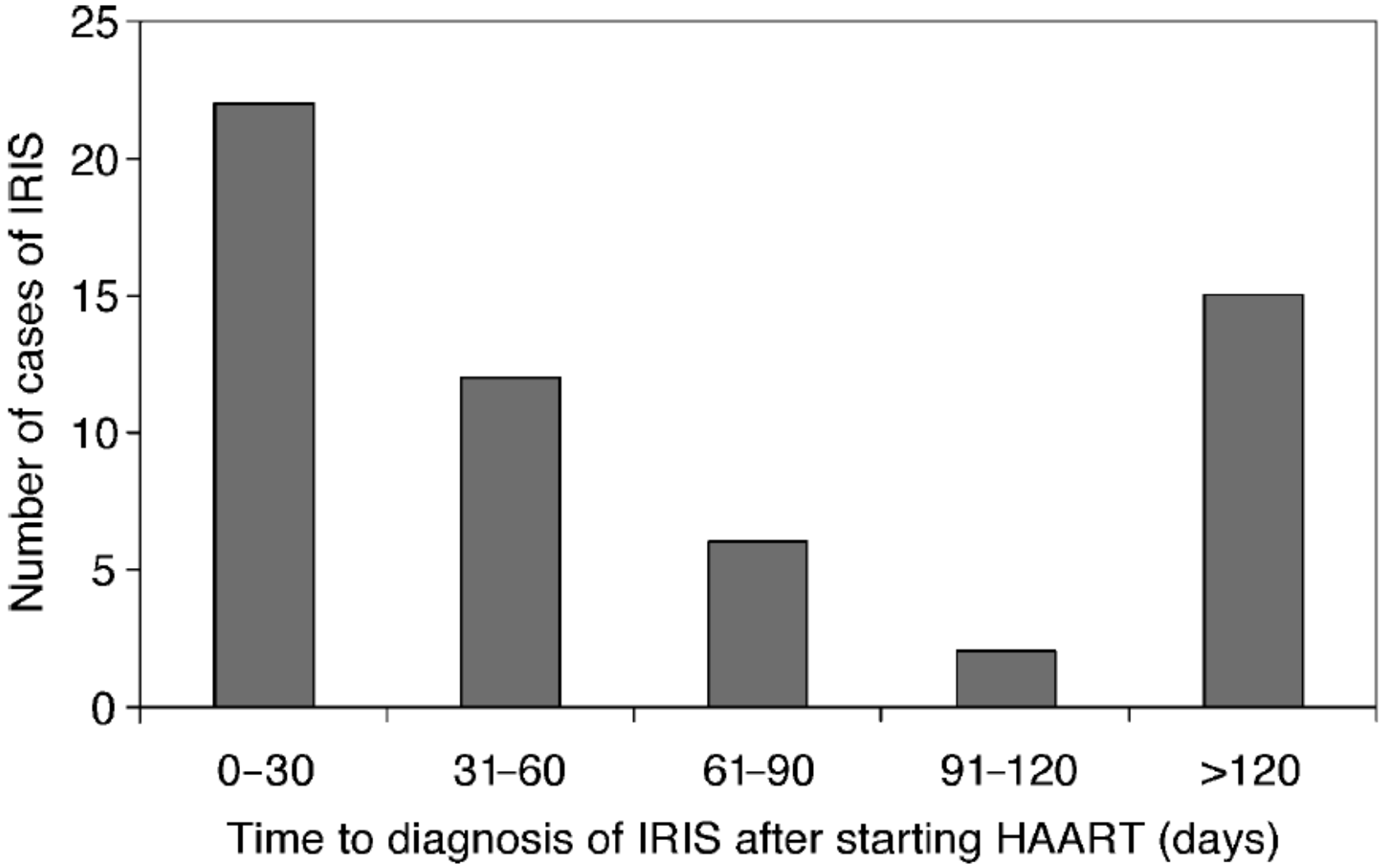
Immune Reconstitution Inflammatory Syndrome (IRIS)

- TB: fever, lymphadenopathy, worsening of lung lesions
- MAC: lymphadenopathy, worsening of skin lesions
- PCP: pneumonitis
- CMV: vitritis, neovascularization, retinal detachment, pneumonitis
- Cryptococcosis: lymphadenopathy, pneumonitis, aseptic meningitis
- Histoplasmosis: pneumonitis, cerebral lesions
- PML: worsening of cerebral lesions

Incidence and risk factors for IRIS

- Shelburne, et al. AIDS 2005; 19: 399-406.
  - A retrospective chart review from 1997-2000 in Houston, Texas
  - 180 HIV patients with TB, MAC, or *C. neoformans* and HAART
  - 31.7% developed IRIS

Time to diagnosis of IRIS



Risk factors for IRIS

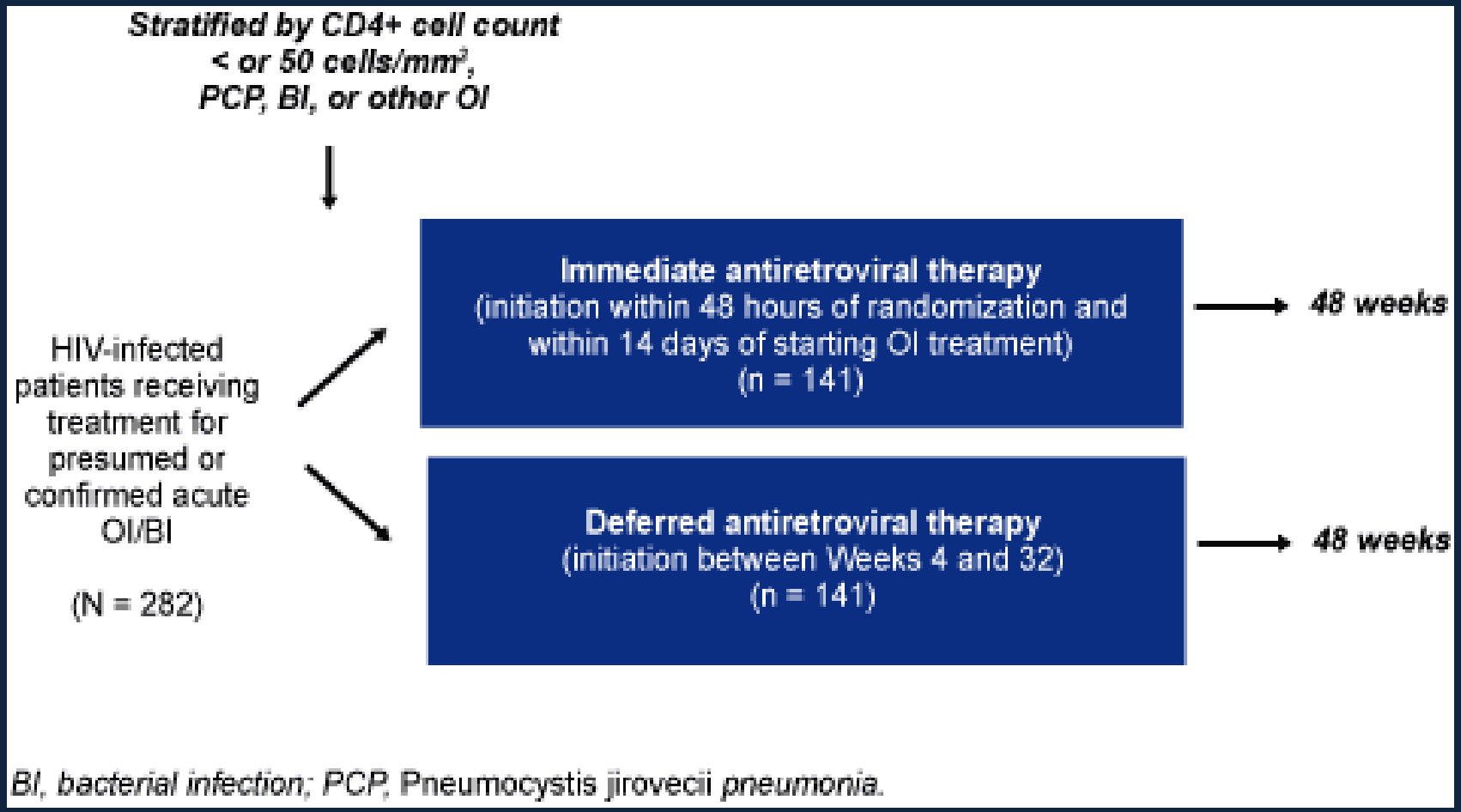
Characteristic	Patients with IRIS	Patients without IRIS	*P* value for difference
No.	57	123	
Underlying opportunistic infection (No.)	57	123	
M. tuberculosis	26	60	
M. avium complex	11	24	0.897
C. neoformans	20	39	
Age at starting HAART (years)	38.5	38.9	0.39
Ethnicity (%)			
White, non-Hispanic	26	26	
Black, non-Hispanic	49	48	0.5519
White Hispanic	23	25	
Other	2	0	
Gender (male %)	93	79	0.018
Median CD4 cell count prior to HAART ($\times 10^6$ cells/l)	30	33	0.529
Median HIV-1 RNA level prior to HAART ($\log_{10}$ copies/ml)	5.40	5.32	0.091
Median interval between initiating treatment for opportunistic infection and starting HAART (days)	27	50	< 0.001
Antiretroviral drug naive at time of diagnosis of underlying opportunistic infection (%)	93	69	< 0.001

Cryptococcal IRIS

- Patients who develop cryptococcal IRIS are more likely to be antiretroviral naive and have higher HIV RNA levels
- Appropriate management of IRIS is to continue ART and antifungal therapy (AII)
- In patients with severely symptomatic IRIS, short-course corticosteroids are recommended (BIII)

NIH, CDC, HIVMA/IDSA Guidelines for prevention and treatment of OI, June 2008

ACTG A5164
Immediate ART Initiation in Patients Presenting With Acute OIs



Zolopa A, et al. PLoS One. 2009;4(5):e5575.

Study design

- Inclusion criteria
  - Presumptive or confirmed AIDS-related OI or BI
    - PCP
    - BI with CD4+ cell count < 200 cells/mm^3
      - Pneumonia, sepsis, deep-seated infections
    - Cryptococcal disease; disseminated histoplasmosis
    - *Mycobacterium avium* complex (MAC), atypical mycobacterial infections
    - Toxoplasmosis, cytomegalovirus (CMV), end organ disease
- No patients with TB were enrolled.

Zolopa A, et al. PLoS One. 2009;4(5):e5575.

Study design

- Primary endpoint
  - 3 ordered categories of clinical and virologic outcomes at Week 48
    - Clinical progression or death (least optimal)
    - Survival without clinical progression; HIV-1 RNA > 50 copies/mL (intermediate)
    - Survival without clinical progression; HIV-1 RNA < 50 copies/mL (most optimal)

Zolopa A, et al. PLoS One. 2009;4(5):e5575.

Study design

- Secondary outcomes
  - Clinical progression or death over 48 weeks
  - Change in HIV-1 RNA and CD4+ cell count over 48 weeks
  - Rates of viral suppression after 24 weeks of antiretroviral therapy
  - Change in CD4+ cell count
  - Safety and tolerability
  - Adherence to antiretroviral therapy
  - Therapy switches, interruptions, and discontinuations

Zolopa A, et al. PLoS One. 2009;4(5):e5575.

Main results

- Median duration from start of OI treatment to initiation of HAART
  - Immediate group: 12 days
  - Deferred group: 45 days
- No significant difference between immediate vs deferred groups in primary endpoint through Week 48 (P = .215)
  - Clinical progression or death: 14.2% vs 24.1%, respectively
  - Survival without clinical progression; HIV-1 RNA > 50 copies/mL: 38.3% vs 31.2%, respectively
  - Survival without clinical progression; HIV-1 RNA < 50 copies/mL: 47.5% vs 44.7%, respectively

Zolopa A, et al. PLoS One. 2009;4(5):e5575.

Secondary outcomes

- Immediate treatment associated with significant reduction in clinical progression or death through Week 48 **(Odds ratio: 0.51 (99% CI: 0.23-1.15), *P* = .035)**
- Immediate treatment associated with shorter time to clinical progression or death **(Hazard ratio: 0.53 (99% CI: 0.25-1.09); *P* = .023)**
- Immediate treatment associated with significantly shorter time to achieving CD4+ cell count > 50 or > 100 cells/mm^3 **(*P* < .001)**

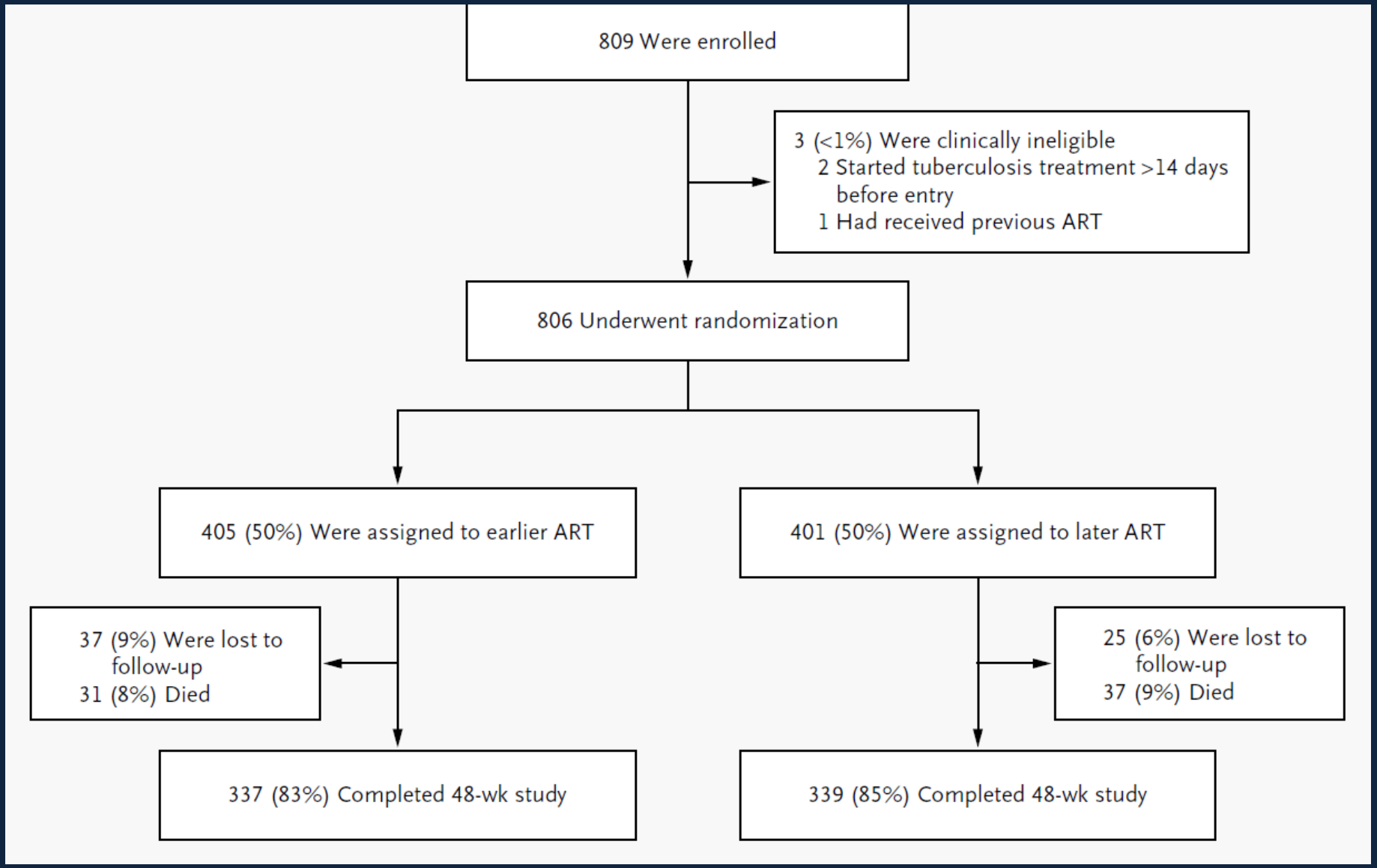
Zolopa A, et al. PLoS One. 2009;4(5):e5575.

Secondary outcomes

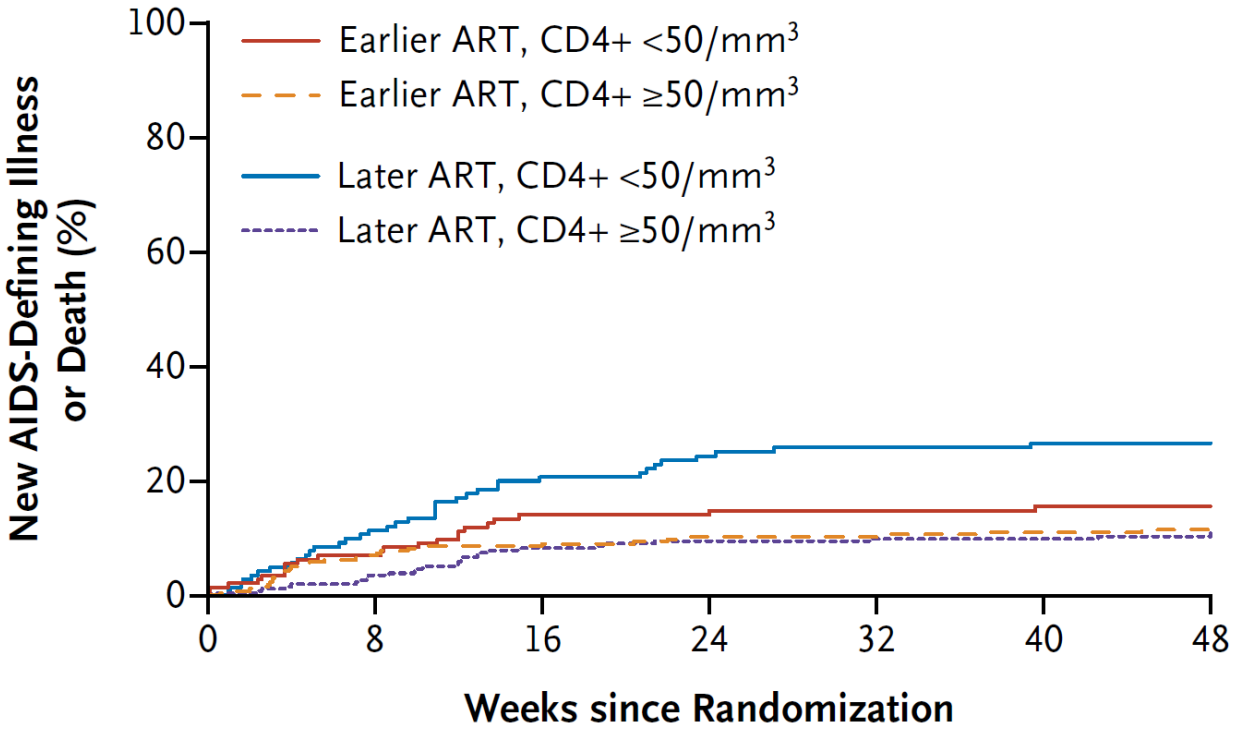
- No significant difference between groups in proportion of patients with HIV-1 RNA < 50 copies/mL at Week 48 (approximately 50% in both arms)
- No significant difference in clinical or laboratory adverse events or hospitalizations between groups over 48 weeks
- IRIS confirmed in 5.7% of immediate group vs 8.5% of deferred group

Zolopa A, et al. PLoS One. 2009;4(5):e5575.

Timing of ART for HIV-1 Infection and Tuberculosis



Timing of ART for HIV-1 Infection and Tuberculosis



No. at Risk

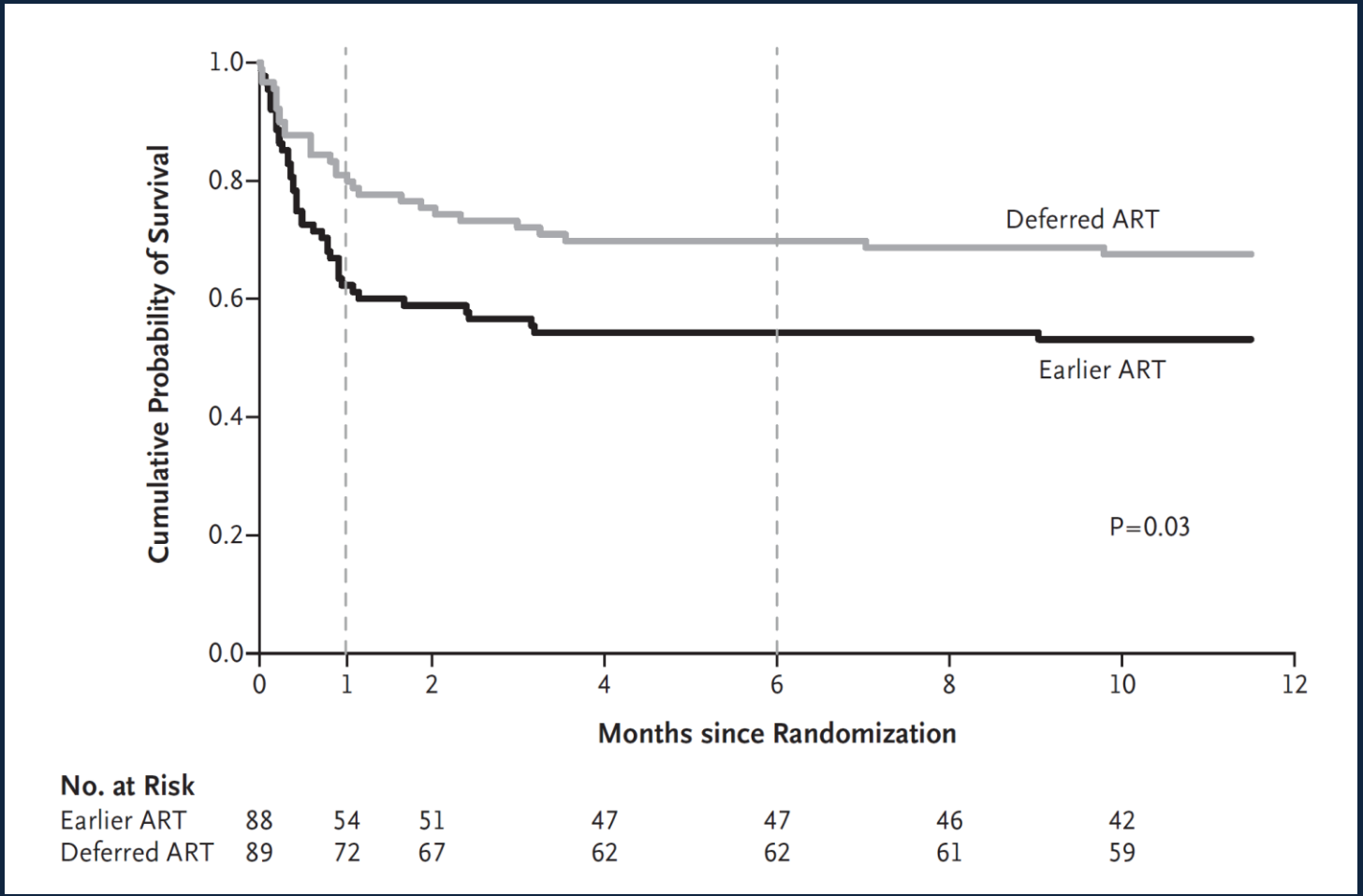
Earlier therapy							
CD4+ <50/mm^3	144	132	121	121	118	114	74
CD4+ ≥50/mm^3	261	236	225	220	217	210	152
Later therapy							
CD4+ <50/mm^3	141	125	110	103	101	98	69
CD4+ ≥50/mm^3	260	246	232	226	224	220	149

Timing of ART for HIV-1 Infection and Cryptococcal Meningitis

- 177 HIV–infected adults in Uganda and South Africa who had cryptococcal meningitis and had not previously received ART.
- Randomly assigned to 1) earlier ART initiation (1 to 2 weeks after diagnosis) or 2) deferred ART initiation (5 weeks after diagnosis)
- Participants received amphotericin B (0.7 to 1.0 mg per kilogram of body weight per day) and fluconazole (800 mg per day) for 14 days, followed by consolidation therapy with fluconazole
- Assessed survival at 26 weeks

Boulware, et al. N Engl J Med 2014;370:2487-98.

Cumulative Probability of Survival According to Timing of ART in HIV with cryptococcal meningitis



Boulware, et al. N Engl J Med 2014;370:2487-98.

Appropriate time to initiate HAART in patients with acute OI

- In patients who have OI for which no effective therapy exists, treatment should be started as soon as possible **(AIII)**.
- For patients with mild to moderate cutaneous KS, prompt initiation of ART alone without chemotherapy has been associated with improvement of the KS lesions.

DHHS guidelines, January 2016

Appropriate time to initiate HAART in patients with acute OI

- In the setting of some OIs, such as cryptococcal and TB meningitis, for which immediate therapy may increase the risk of serious IRIS, a short delay before initiating ART may be warranted
- In the setting of other OIs, such as PCP, early initiation of ART is associated with increased survival; therefore, therapy should not be delayed **(AI)**

DHHS guidelines, January 2016

TB and HIV Coinfection: ART Recommendations

- Immediately initiate TB treatment **(AI)**
- All patients should be treated with ART **(AI)**
  - Start ART within 2 weeks if CD4<50 cells/µL **(AI)**
  - Start ART within 2-4 weeks if CD4>50 cells/µL with severe disease
    - who have CD4 count 50-200 cells/µL **(BI)**
    - CD4 count >200 cells/µL **(BIII)**
  - ART can be delayed to 8-12 weeks if CD4>50 cells/µL with mild disease
    - CD4 count 50-500 cells/µL **(AI)**
    - CD4>500 **(BIII)**

DHHS guidelines, January 2016

Appropriate time to initiate HAART in patients with acute OI

โรคติดเชื้อฉวยโอกาส	ระดับ CD4 (cells/mm^3)		
	≤ 50	> 50	
วัณโรค (Tuberculosis)	ภายใน 2 สัปดาห์	รุนแรง*	ไม่รุนแรง
		ภายใน 2 สัปดาห์	ระหว่าง 2-8 สัปดาห์
Cryptococcosis	ระหว่าง 4-6 สัปดาห์		
PCP/MAC/อื่น ๆ	ระหว่าง 2-4 สัปดาห์		
CMV/PML/Cryptosporidium	ควรพิจารณาเริ่มให้ยาต้านไวรัสกับผู้ป่วยเร็วที่สุดเท่าที่จะทำได้		

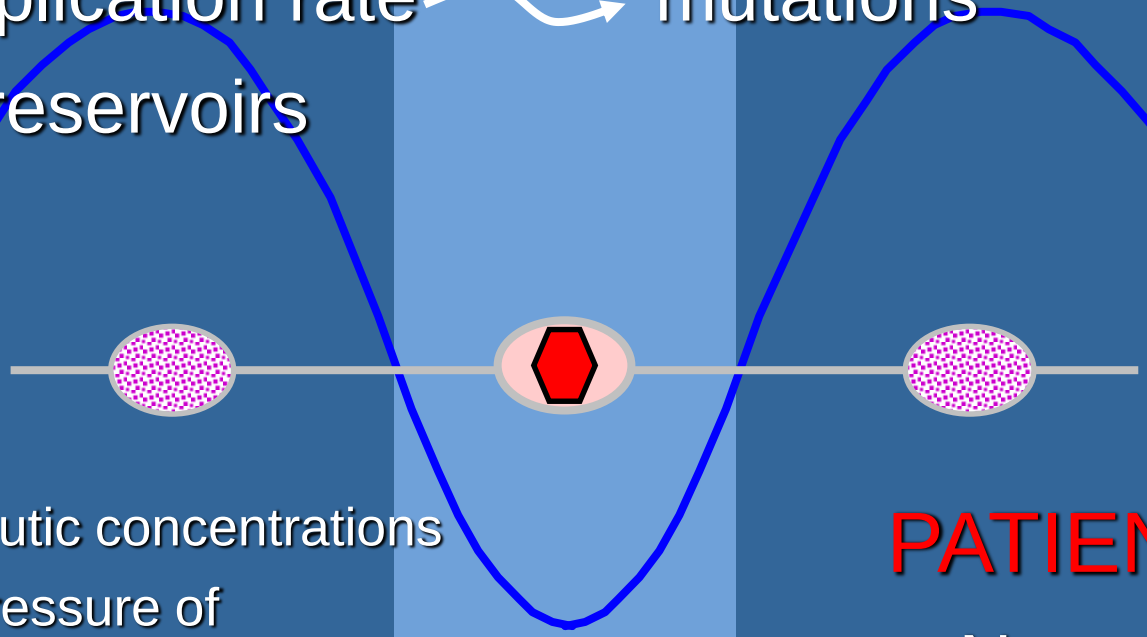
Thai Guidelines, Sep 2014

HIV Treatment failure

Development of Viral Resistance

VIRUS

- High replication rate ⇝ mutations
- Latent reservoirs



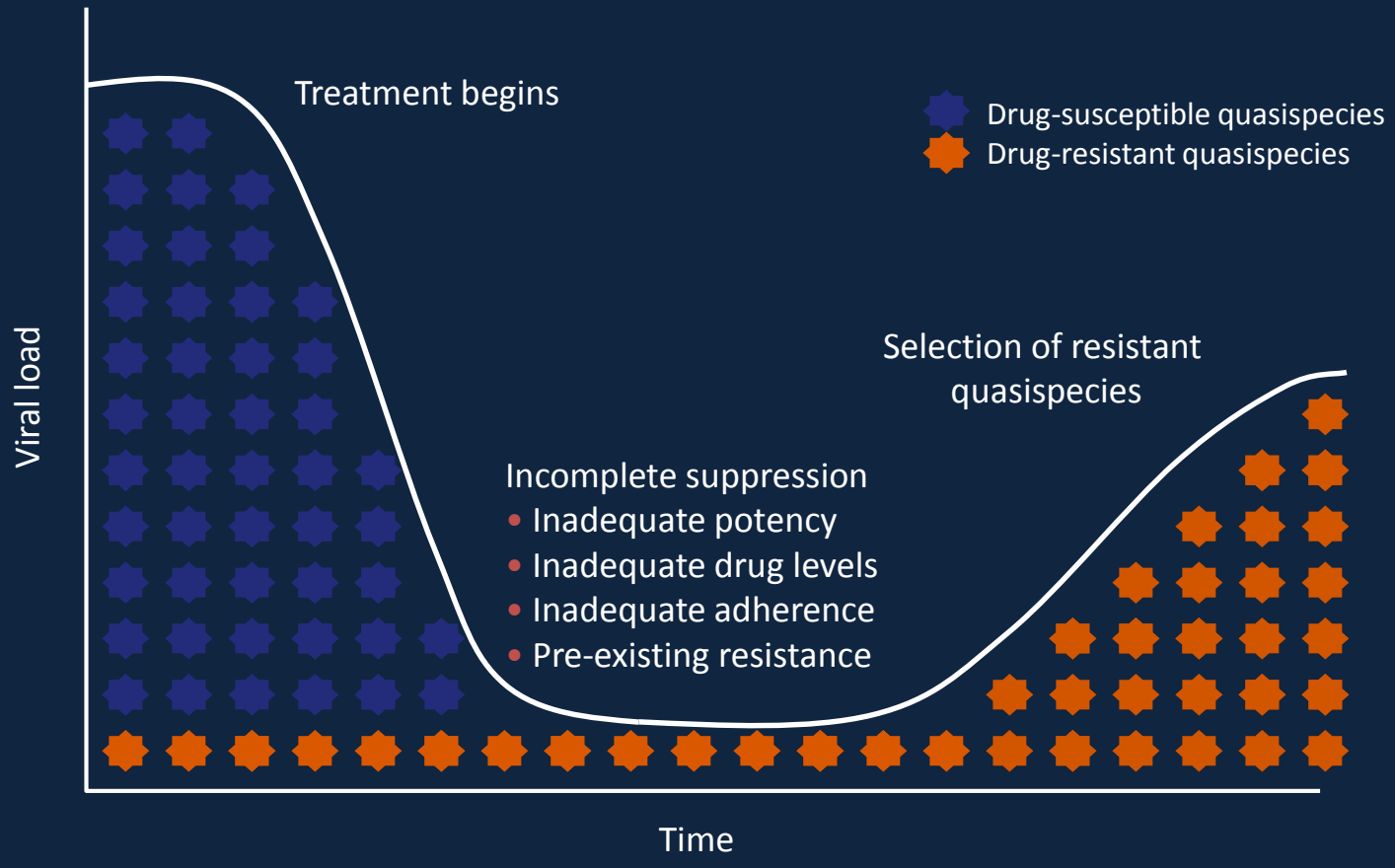
DRUG

- Subtherapeutic concentrations
- Selective pressure of less potent ARV therapy

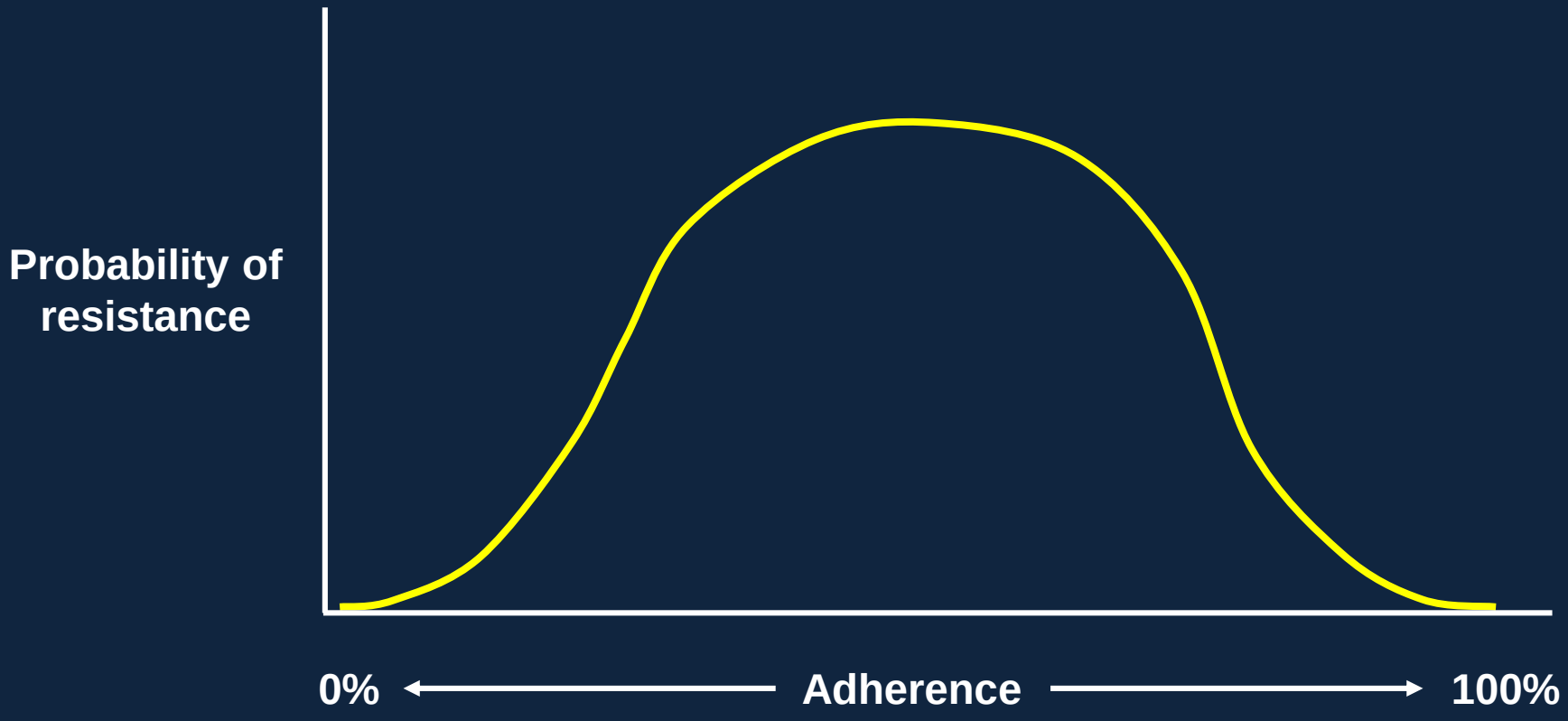
PATIENT

- Nonadherence
- Side effects

Selective Pressures of Therapy

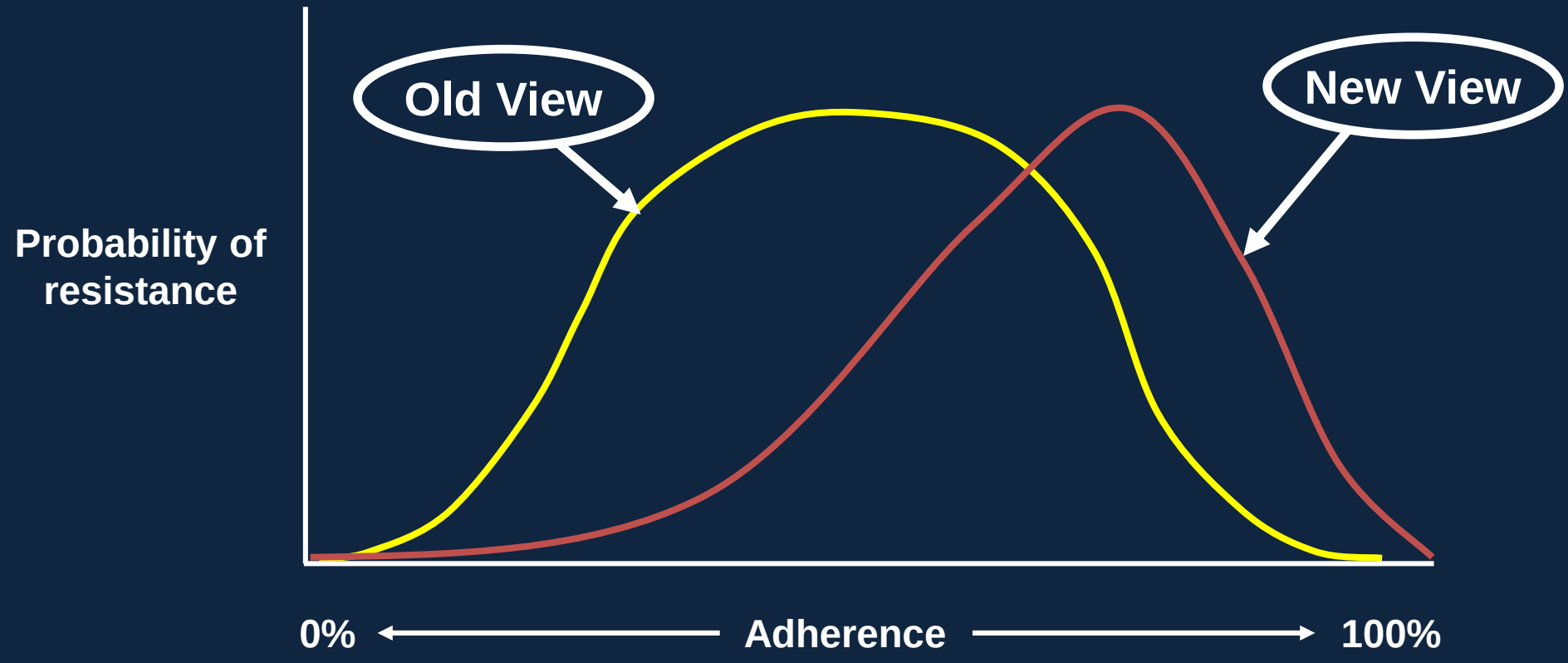


Adherence and Emergence of Resistant Virus Strains



Based on Friedland GH, et al. 1999;13(suppl 1):S61-S71.

Adherence and Emergence of Resistant Virus Strains



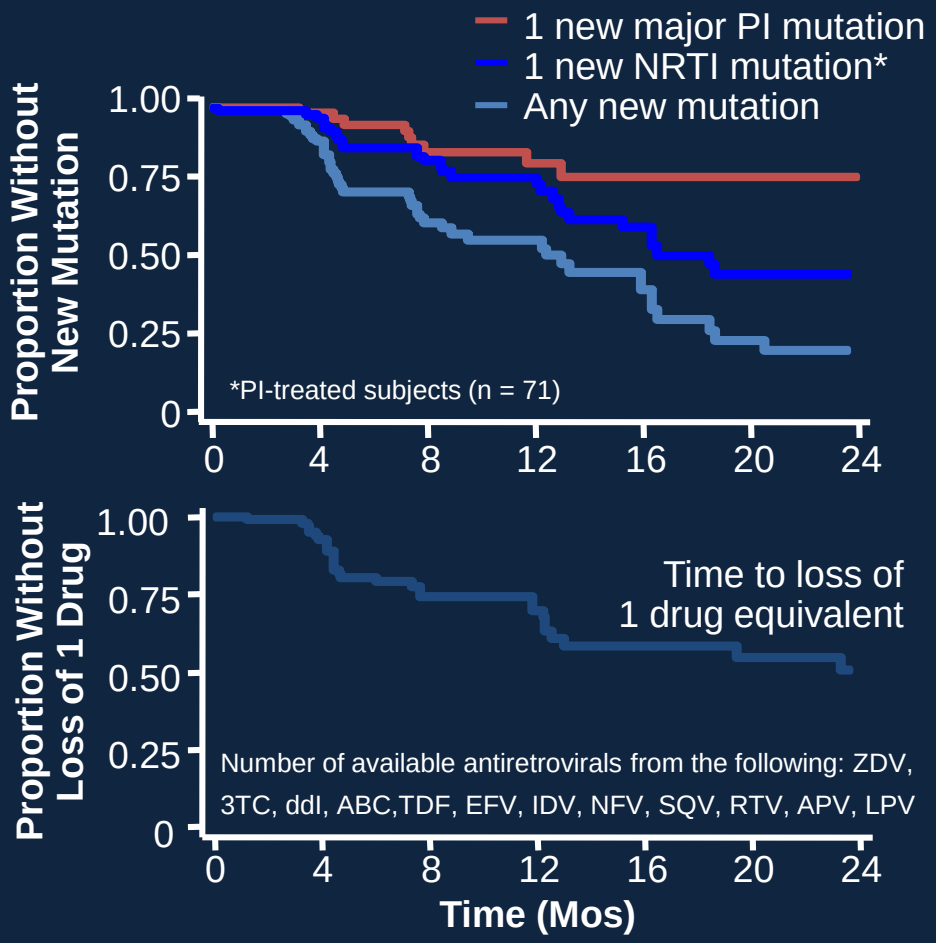
Based on Friedland GH, et al. 1999;13(suppl 1):S61-S71.

การดื้อต่อยาต้านไวรัสเอดส์

- เชื้อสามารถดื้อต่อยาบางชนิดโดยอาศัยการกลายพันธุ์เพียงตำแหน่งเดียว เช่น 3TC, NNRTI
- การดื้อยาบางชนิดต้องการการกลายพันธุ์หลายตำแหน่งและมักเกิดขึ้นช้า ๆ เช่น ZDV, PI
- การให้ผู้ป่วยกินยาที่ไม่ได้ผลต่อไป จะทำให้เชื้อกลายพันธุ์มากขึ้นจนเกิดการดื้อต่อยาในกลุ่มเดียวกัน

การให้ผู้ป่วยกินยาที่ไม่ได้ผลต่อไป

- SCOPE cohort of ART-experienced subjects (n = 106)
  - HIV RNA > 1000 c/mL
  - ≥ 1 resistance mutation
- Emergence of new mutations at 1 yr
  - Any mutation = 44% (95% CI: 33% to 56%)
  - NAM = 23% (95% CI: 15% to 34%)
  - PI = 18% (95% CI: 9% to 34%)



Hatano H, et al. CROI 2006. Abstract 615.

การตรวจการดื้อยา ARV

- ช่วยในการตัดสินใจเลือกยา ARV
- เพื่อให้ได้ประโยชน์สูงสุด ต้องอาศัยข้อมูลอื่นร่วมด้วย
  - ประวัติการกินยา ARV
  - การตอบสนองต่อยาเดิม
  - ภาวะภูมิต้านทานของผู้ป่วย
  - ข้อมูลทางเภสัชวิทยา
  - ความรู้ของแพทย์เกี่ยวกับ ARV

ข้อบ่งชี้ในการตรวจการดื้อยา ARV

- Acute HIV infection
- Chronic HIV infection
- Patients with virologic failure
- Patients with suboptimal suppression of viral load
- HIV-infected pregnant women

DHHS guidelines, January 2016

การตรวจการดื้อยา ARV

- ไม่แนะนำให้ทำในกรณีต่อไปนี้
  - ผู้ป่วยที่มีเชื้อ HIV ในเลือด <500/ml
  - ผู้ป่วยที่หยุดกินยา ARV

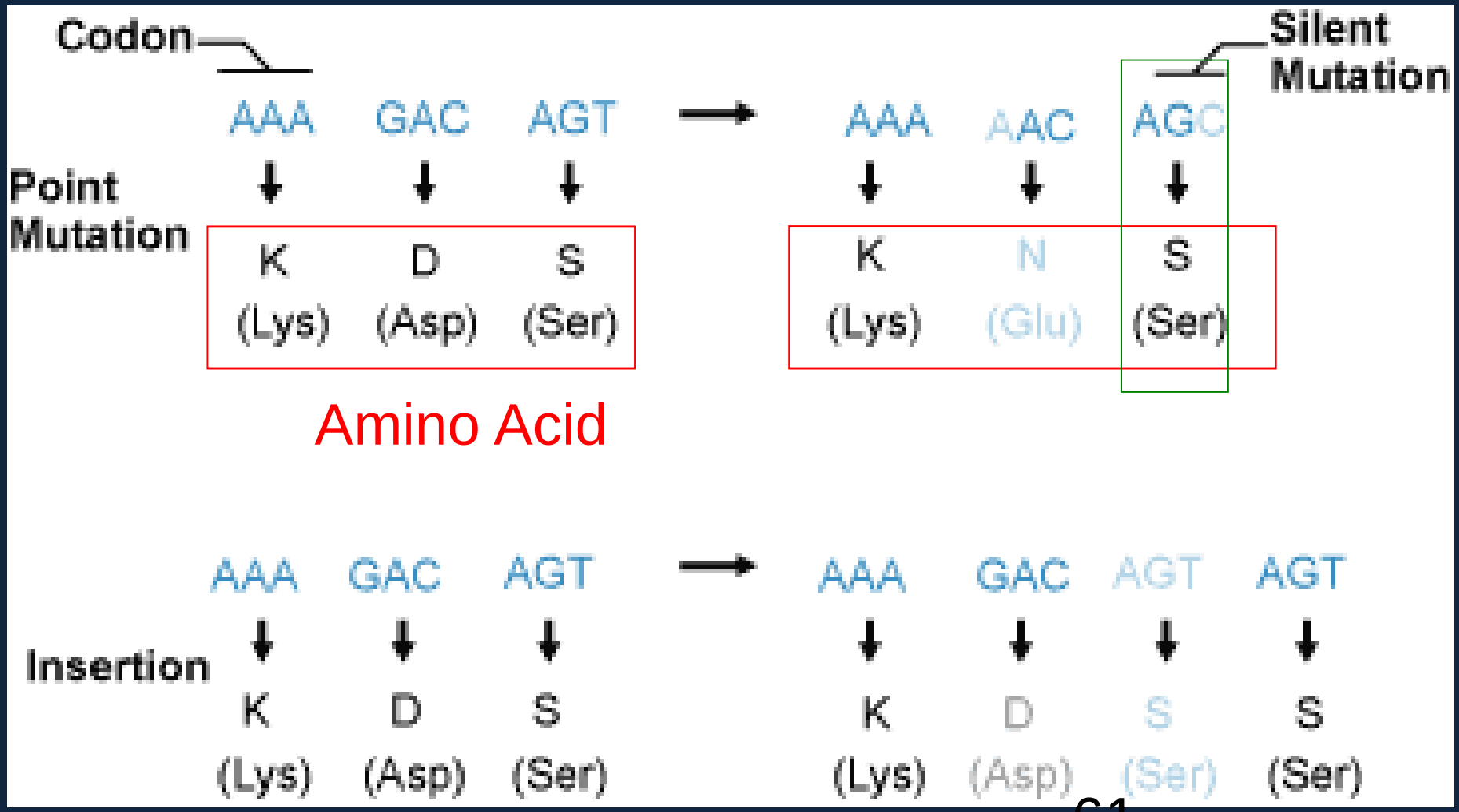
วิธีการตรวจการดื้อยา ARV

- Genotype assays
  - แสดงตำแหน่งที่เกิด mutations ซึ่งอาจทำให้ดื้อต่อยา
- Phenotype assays
  - ตรวจความไวต่อยาโดยตรง แสดงความแตกต่างระหว่างเชื้อจากตัวผู้ป่วยกับเชื้ออ้างอิง
- Virtual phenotype combined G+P databases

การแปลผลการตรวจการดื้อยา

- การแปลผล Genotypic tests คล้ายกับ EKG, biopsy, MRI
- แพทย์ไม่จำเป็นต้องจำ drug resistance mutations ให้ได้ทั้งหมด
- การแปลผล Phenotypic tests คล้ายการตรวจ antimicrobial susceptibility test แต่อาจไม่ตรงไปตรงมาทุกกรณี เช่น 5-fold resistance ต่อ 3TC ไม่เท่ากับ 5-fold resistance ต่อ d4T

การกลายพันธุ์ของ HIV



Mutation Nomenclature

Codon (position)
PR = 1-99 amino acids
RT = 1-560 amino acids

M184V

Mutation Nomenclature

Codon (position)
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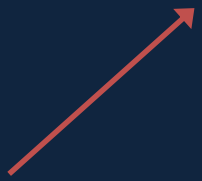
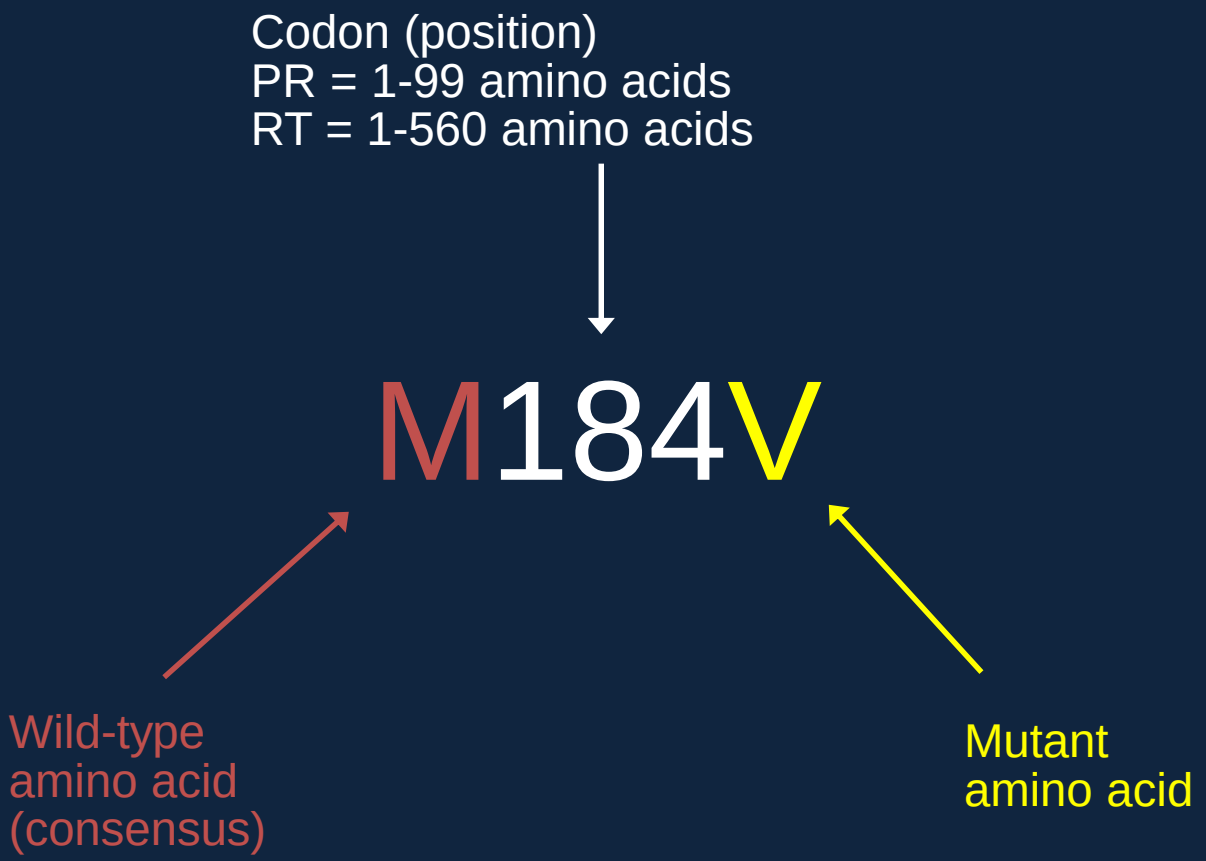
M184V



Wild-type
amino acid
(consensus)

Mutation Nomenclature



ฐานข้อมูลที่ใช้ในการแปลผล

- The International AIDS Society-USA
  https://www.iasusa.org/content/drug-resistance-mutations-in-HIV
- Stanford HIV RT and Protease Sequence Database
  http://hivdb.stanford.edu

Mutations in the Reverse Transcriptase Gene Associated With Resistance to Reverse Transcriptase Inhibitors (cont'd)

	41	65	67	70	74	115	184	210	215	219
Abacavir		K 65 R, E, N			L 74 V	Y 115 F	M 184 V			
Didanosine		K 65 R, E, N			L 74 V					
Emtricitabine		K 65 R, E, N					M 184 V, I			
Lamivudine		K 65 R, E, N					M 184 V, I			
Stavudine	M 41 L	K 65 R, E, N	D 67 N	K 70 R				L 210 W	T 215 Y, F	K 219 Q, E
Tenofovir		K 65 R, E, N		K 70 E						
Zidovudine	M 41 L		D 67 N	K 70 R				L 210 W	T 215 Y, F	K 219 Q, E

https://www.iasusa.org/content/drug-resistance-mutations-in-HIV

Mutations in the Reverse Transcriptase Gene Associated With Resistance to Reverse Transcriptase Inhibitors

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)

Multi-nRTI Resistance: 69 Insertion Complex (affects all nRTIs currently approved by the US FDA)

M	A	▼	K	L	T	K
41	62	69	70	210	215	219
L	V	Insert	R	W	Y	Q
					F	E

Multi-nRTI Resistance: 151 Complex (affects all nRTIs currently approved by the US FDA except tenofovir)

A	V	F	F	Q
62	75	77	116	151
V	I	L	Y	M

Multi-nRTI Resistance: Thymidine Analogue-Associated Mutations (TAMs; affect all nRTIs currently approved by the US FDA)

M	D	K	L	T	K
41	67	70	210	215	219
L	N	R	W	Y	Q
				F	E

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Mutations in the Reverse Transcriptase Gene Associated With Resistance to Reverse Transcriptase Inhibitors (cont'd)

Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)

Efavirenz

L	K	K	V	V	Y	Y	G	P	M
100	**101**	**103**	**106**	**108**	**181**	**188**	**190**	**225**	**230**
I	**P**	**N**	**M**	**I**	**C**	**L**	**S**	**H**	**L**
		S			**I**		**A**		

Etravirine

V	A	L	K	V	E	V	Y	G	M
90	98	**100**	**101**	106	138	179	**181**	190	230
I	G	**I***	E	I	A	D	**C***	S	L
			H		G	F	**I***	A	
			P*		K	T	**V***		
					Q				

Nevirapine

L	K	K	V	V	Y	Y	G	M
100	**101**	**103**	**106**	**108**	**181**	**188**	**190**	**230**
I	**P**	**N**	**A**	**I**	**C**	**C**	**A**	**L**
		S	**M**		**I**	**L**		
						H		

Rilpivirine

L	K	E	V	Y	Y	H	F	M
100	**101**	**138**	**179**	**181**	**188**	**221**	**227**	**230**
I	**E**	**A**	**L**	**C**	**L**	**Y**	**C**	**I**
	P	**G**		**I**				**L**
		K		**V**				
		Q						
		R						

https://www.iasusa.org/content/drug-resistance-mutations-in-HIV

Mutations in the Protease Gene Associated With Resistance to Protease Inhibitors

Atazanavir +/-ritonavir

L	G	K	L	V	L	E	M	M	G	I	F	I	D	I	I	A	G	V	I	I	N	L	I
10	16	20	24	32	33	34	36	46	48	**50**	53	54	60	62	64	71	73	82	**84**	85	**88**	90	93
I	E	R	I	I	I	Q	I	I	V	L	L	L	E	V	L	V	C	A	V	V	S	M	L
F		M			F		L	L			Y	V			M	I	S	T					M
V		I			V		V					M			V	T	T	F					
C		T										T				L	A	I					
		V										A											

Darunavir/ ritonavir

V	V	L	I	I	I	T	L	I	L
11	32	33	**47**	**50**	**54**	74	**76**	**84**	89
I	I	F	V	V	M	P	V	V	V
					L				

Fosamprenavir/ ritonavir

L	V	M	I	I	I	G	L	V	I	L
10	32	46	47	**50**	54	73	76	82	**84**	90
F	I	I	V	V	L	S	V	A	V	M
I		L			V			F		
R					M			S		
V								T		

Indinavir/ ritonavir

L	K	L	V	M	M	I	A	G	L	V	V	I	L
10	20	24	32	36	**46**	54	71	73	76	77	**82**	**84**	90
I	M	I	I	I	I	V	V	S	V	I	A	V	M
R	R				L		T	A			F		
V											T		

Lopinavir/ ritonavir

L	K	L	V	L	M	I	I	F	I	L	A	G	L	V	I	L
10	20	24	**32**	33	46	**47**	50	53	54	63	71	73	**76**	**82**	84	90
F	M	I	I	F	I	V	V	L	V	P	V	S	V	A	V	M
I	R				L	A			L		T			F		
R									A					T		
V									M					S		
									T							
									S							

https://www.iasusa.org/content/drug-resistance-mutations-in-HIV

Mutations in the Protease Gene Associated With Resistance to Protease Inhibitors (cont'd)

Nelfinavir

L	D	M	M	A	V	V	I	N	L
10	**30**	36	46	71	77	82	84	88	**90**
F	N	I	I	V	I	A	V	D	M
I			L	T		F		S	
						T			
						S			

Saquinavir/ ritonavir

L	L	G	I	I	A	G	V	V	I	L
10	24	**48**	54	62	71	73	77	82	84	**90**
I	I	V	V	V	V	S	I	A	V	M
R			L		T			F		
V								T		
								S		

Tipranavir/ ritonavir

L	L	M	K	M	I	I	Q	H	T	V	N	I	L
10	33	36	43	46	**47**	54	**58**	69	**74**	**82**	**83**	**84**	89
V	F	I	T	L	V	A	E	K	P	L	D	V	I
		L				M		R		T			M
		V				V							V

https://www.iasusa.org/content/drug-resistance-mutations-in-HIV

Mutations in the Envelope Gene Associated With Resistance to Entry Inhibitors

Enfuvirtide

G	I	V	Q	Q	N	N
36	37	38	39	40	42	43
D	V	A	R	H	T	D
S		M				
		E				

Maraviroc

See User Note

User Notes available at www.iasusa.org

https://www.iasusa.org/content/drug-resistance-mutations-in-HIV

Mutations in the Integrase Gene Associated With Resistance to Integrase Strand Transfer Inhibitors

Dolutegravir

F	E	G	Q	N	R
121	138	140	**148**	155	263
Y	A	A	**H**	H	K
	K	S	**R**		

Elvitegravir

T	E	T	F	S	Q	N	R
66	**92**	97	**121**	**147**	**148**	**155**	263
I	**Q**	A	**Y**	**G**	**H**	**H**	K
A	G				**K**		
K					**R**		

Raltegravir

L	E	T	F	E	G	Y	Q	N	R
74	92	97	**121**	138	140	**143**	**148**	**155**	263
M	Q	A	**Y**	A	A	**R**	**H**	**H**	K
				K	S	**H**	**K**		
						C	**R**		

https://www.iasusa.org/content/drug-resistance-mutations-in-HIV

Assessment of Virologic Failure

- Suboptimal Adherence
- Medication Intolerance
- Pharmacokinetic Issues
- Suspected Drug Resistance
  - Perform resistance testing while the patient is still taking the failing regimen or within 4 weeks of regimen discontinuation if the patient's plasma HIV RNA level is >1,000 copies/mL (AI)

DHHS guidelines, January 2016

Approach to Patients with Confirmed Virologic Failure

- The goal of treatment is to establish virologic suppression **(AI)**
- New ARV regimen should contain at least 2, and preferably 3, fully active drugs **(AI)**
- Adding a single ARV agent is **not** recommended **(BII)**
- If maximal virologic suppression is not possible, ART should be continued **(AI)** with regimens designed to minimize toxicity, preserve CD4 cell counts, and delay clinical progression
- Discontinuing therapy is **not** recommended **(AI)**

DHHS guidelines, January 2016

Questions?

Thank you for your attention