

HIV/AIDS: NOW and Later

Veronica Jenkins, MD
vjenkins@fmcsinc.org

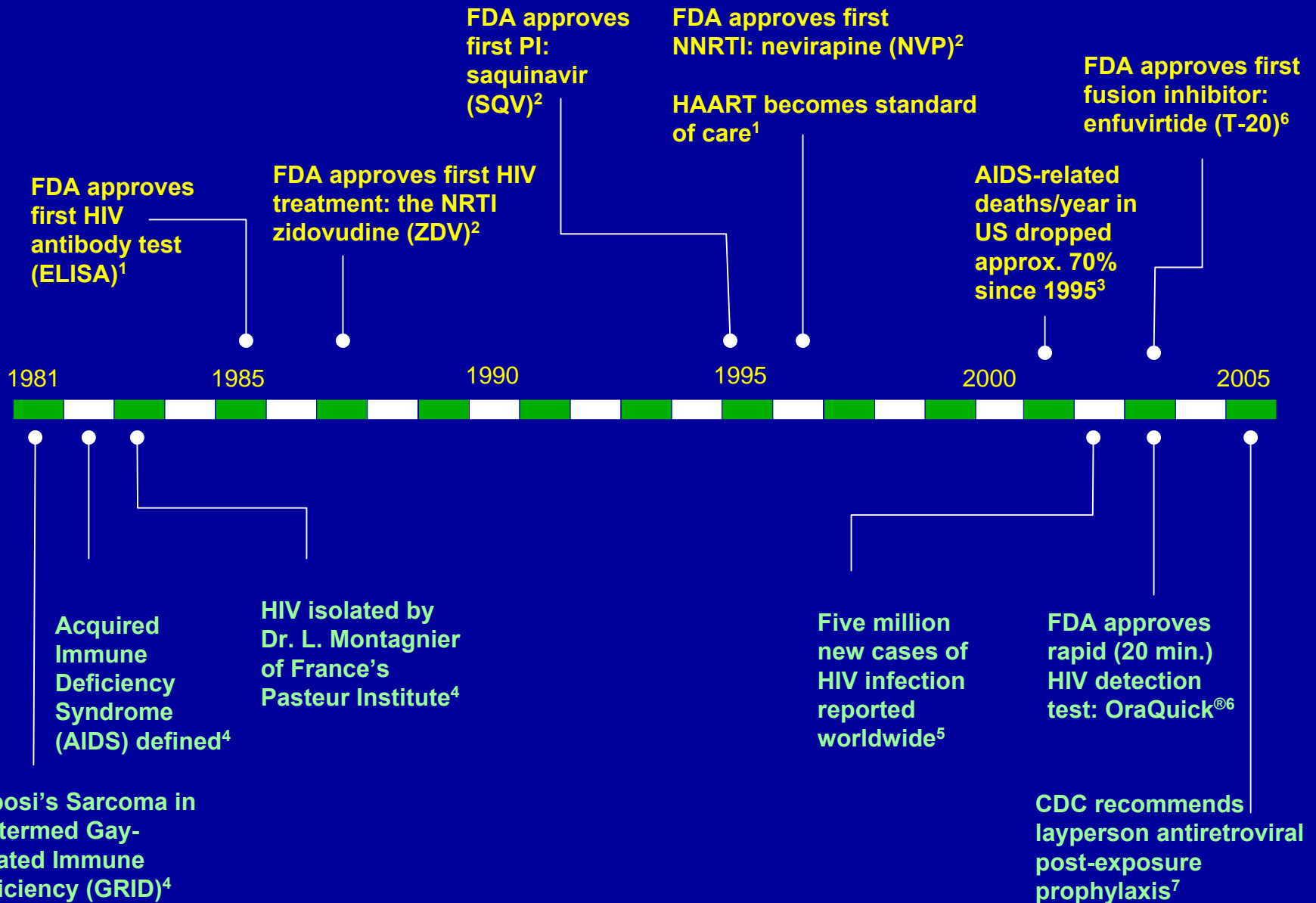
Course Objectives

- Review Treatment Options
- Review DHHS recommendations
- Discuss novel medicines
- Discuss treatment obstacles in today's client

HIV/AIDS: 1995

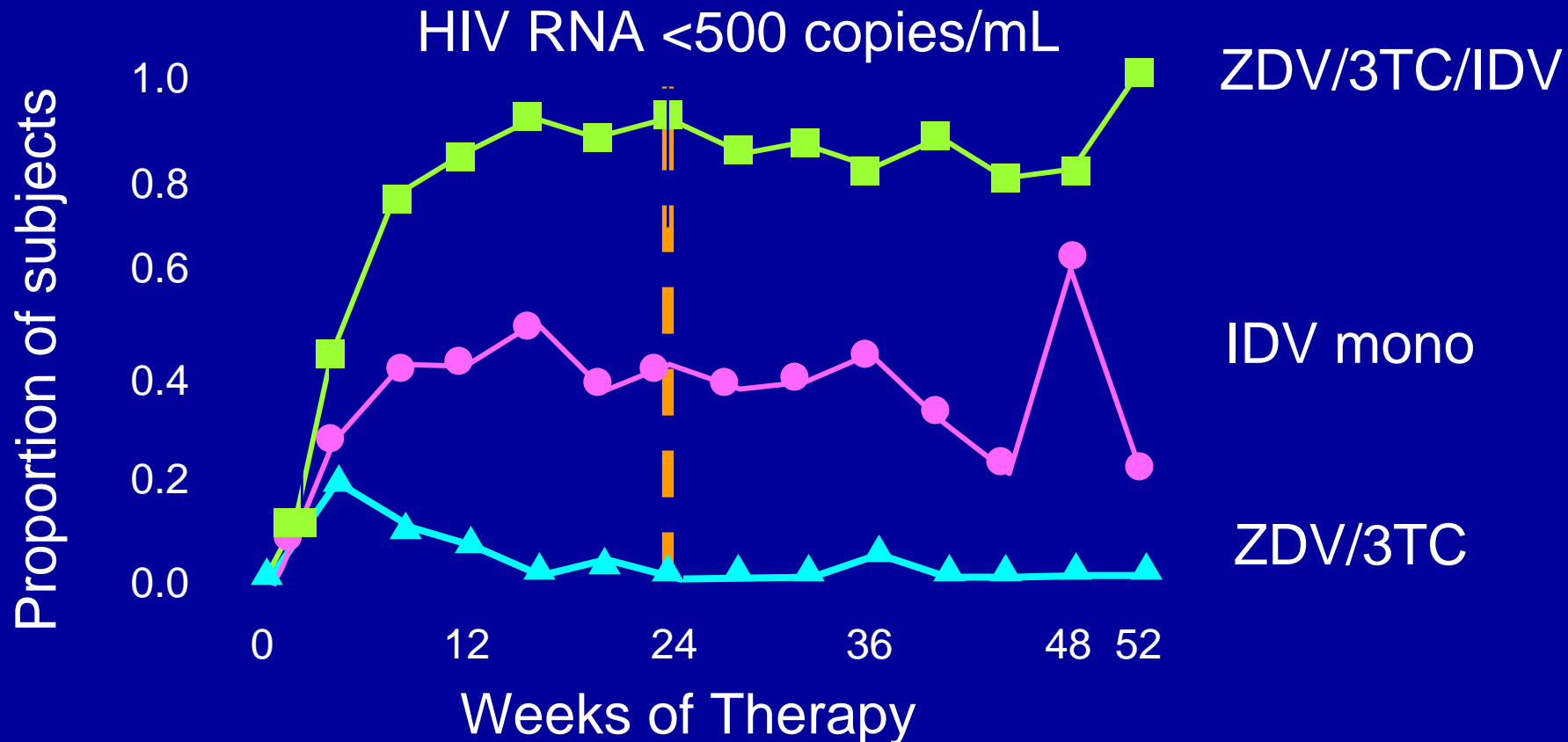
- 4 approved antiretroviral drugs:
ZDV, ddI, ddC, d4T
- 3TC in expanded access
- HIV protease inhibitors in clinical trials:
SQV, RTV, IDV
- Standard of care: dual nucleoside therapy
 - ACTG 175 and Delta studies: dual nucleoside survival benefit (over monotherapy) Hammer SM et al. *N Engl J Med.* 1996;335:1081-1090. Delta Coordinating Committee. *Lancet.* 1996;348:283-291.
 - NUCA studies: ZDV + 3TC potent and well-tolerated Eron JJ et al. *N Engl J Med.* 1995;333:1662-1669
Bartlett JA et al. *Ann Intern Med.* 1996;125:161-172.

HIV Timeline

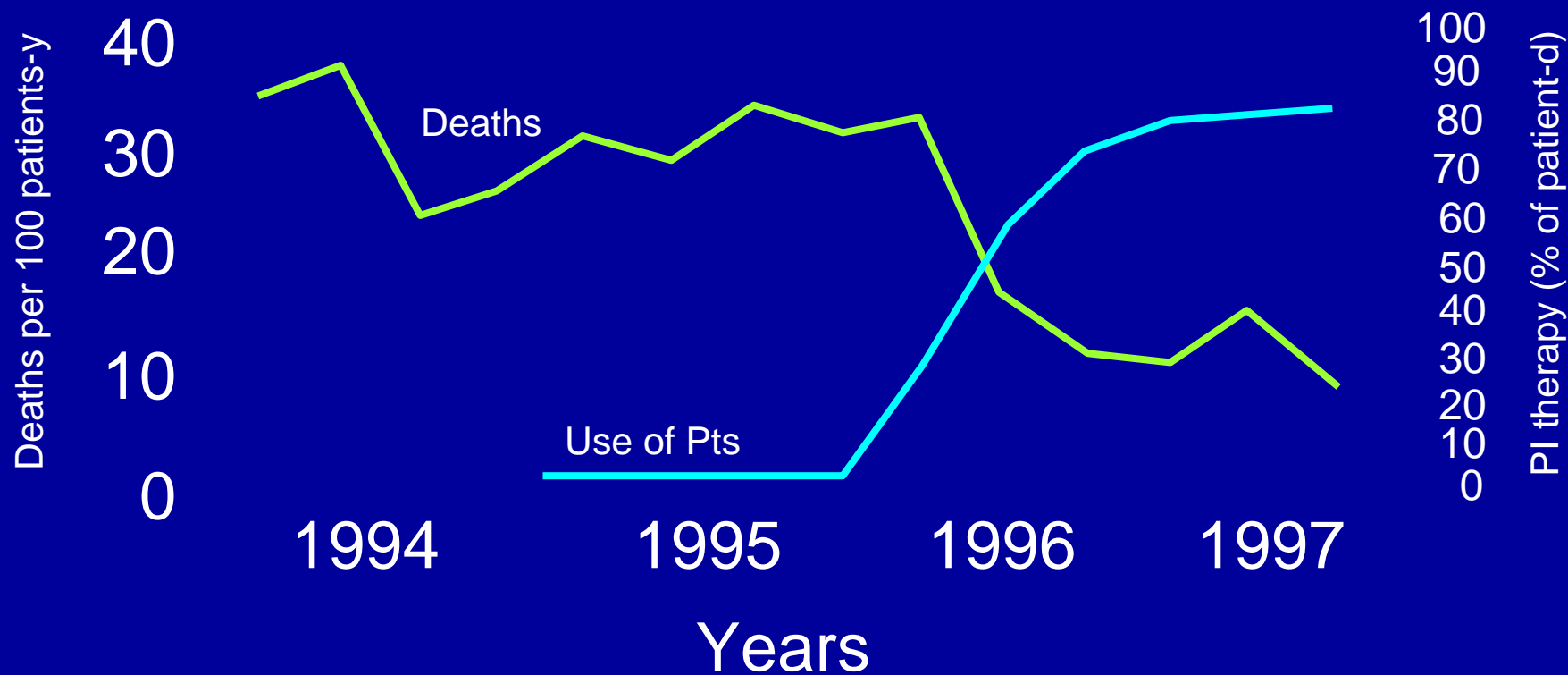


Merck 035 Study Results: CROI 1996

N=97, ZDV-experienced, HIV RNA >20K copies/mL,
CD4 count 50-400/mm³

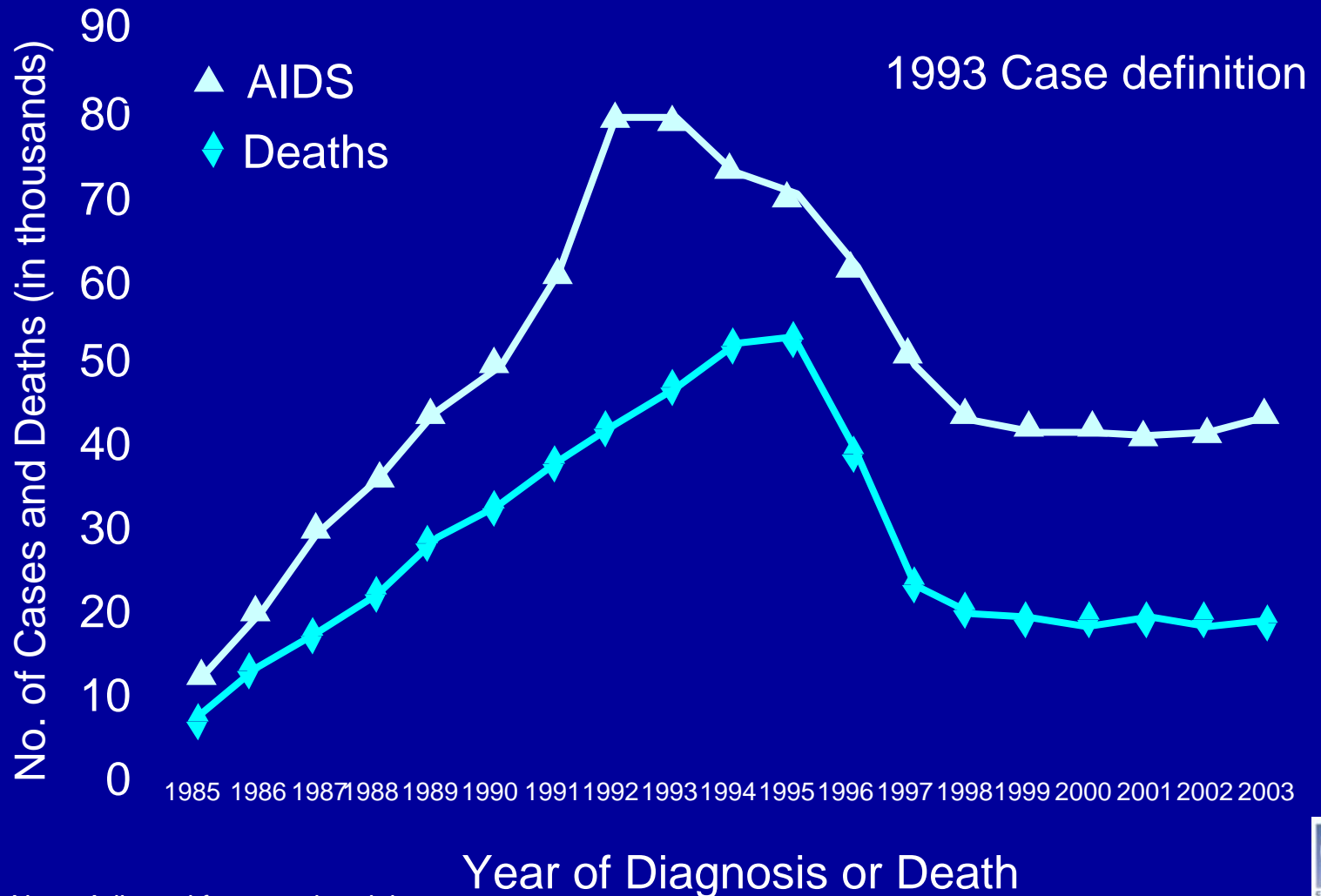


Mortality and Frequency of Use of ART including PI Among HIV-infected Patients With CD4 Counts <100 Cells/ μ L*



*Quarterly from January 1994-June 1997.

Estimated Number of AIDS Cases and Deaths Among Adults and Adolescents with AIDS, 1985–2003—United States



Note: Adjusted for reporting delays



DHHS Guidelines: 1998

Preferred:

Column A

- IDV
- NFV
- RTV
- SQV sgc
- RTV + SQV

Column B

- ZDV + ddl
- d4T + ddl
- ZDV + ddC
- ZDV + 3TC
- d4T + 3TC

Alternative: NVP or SQV hgc

Not generally recommended: 2 NRTI

DHHS Guidelines: 2002

Strongly recommended:

Column A

- EFV
- IDV
- NFV
- RTV + IDV
- RTV + LPV
- RTV + SQV

Column B

- ddl + 3TC
- d4T + ddl
- d4T + 3TC
- ZDV + ddl
- ZDV + 3TC

Alternatives: ABC, APV, DLV, NFV + SQV, NVP, RTV, SQV-sgc and ZDV + ddC

DHHS 2005

- Preferred PI regimen:
 - Kaletra

- Preferred NNRTI
 - Sustiva

Medications

- 3TC (Lamivudine, Epivir)
Abacavir (Ziagen)
Amprenavir (Agenerase)
Atazanavir (Reyataz)
AZT (Zidovudine, Retrovir)
Combivir (AZT/3TC)
d4T (Stavudine, Zerit)
ddC (Zalcitabine, Hivid)
- ddI (Didanosine, Videx)
Delavirdine (Rescriptor)
Efavirenz (Sustiva, Stocrin)

Medications

- FTC (Emtricitabine, Emtriva)
Indinavir (Crixivan)
Kaletra (Lopinavir/Ritonavir)
Nelfinavir (Viracept)
Nevirapine (Viramune)
Ritonavir (Norvir)
Saquinavir (Fortovase, Invirase)
T-20 (Enfuvirtide, Fuzeon)
Tenofovir (Viread)
Tipranavir (Aptivus)
Trizivir (AZT/3TC/abacavir)
Truvada (Tenofovir/FTC)

Advances Using Current Drugs

New
formulations

LPV/r Tablets

ZDV/3TC

Fixed-dose
combinations

ABC/3TC

TDF/FTC/EFV

TDF/FTC

Single class combination
therapy

Quad NRTI

PI + NNRTI

Dual
agents

PI + CCR5

NNRTI + CCR5

Monotherapy

LPV/r

ATV/RTV

Optimization of Current Therapies A5202

Average 3 years follow-up (2009)

NRTIs

3rd Agent

ABC/3TC

EFV

n~1800

TDF/FTC

ATV/RTV

TDF/FTC

EFV

ABC/3TC

ATV/RTV

TDF/FTC

ATV/RTV

ABC/3TC

EFV

Further Refining Therapy with Existing Agents: Studies Within A5202

- Pharmacology
 - Drug levels by gender, ethnicity
 - Levels and virologic response
- Immune reconstitution inflammatory syndrome
 - Epidemiology
 - Predictors
 - Pathogenesis
- Virology
 - Dynamics for emergence of resistance
 - Drug selection effect on subsequent treatment options
- Metabolic substudy
 - Lipoatrophy
 - Lipohypertrophy
 - Bone mineral density
 - Lipids
 - Glucose
 - Renal

Clinical Research Goals for the Next Decade

- Maintain potency while increasing convenience and tolerability and delaying development of resistance
- Define how novel agents fit into current treatment paradigms
- Minimize drug exposure
 - Induction-maintenance
 - Treatment interruptions
 - Alter natural history of disease
- Enhance immune reconstitution
- Improve management of adverse events

Class Sparing

Standard

NRTIs x 2

NNRTI or PI + RTV

PI/NNRTI-sparing

NRTIs x 4

NRTIs x 3

NRTI-sparing

NNRTI

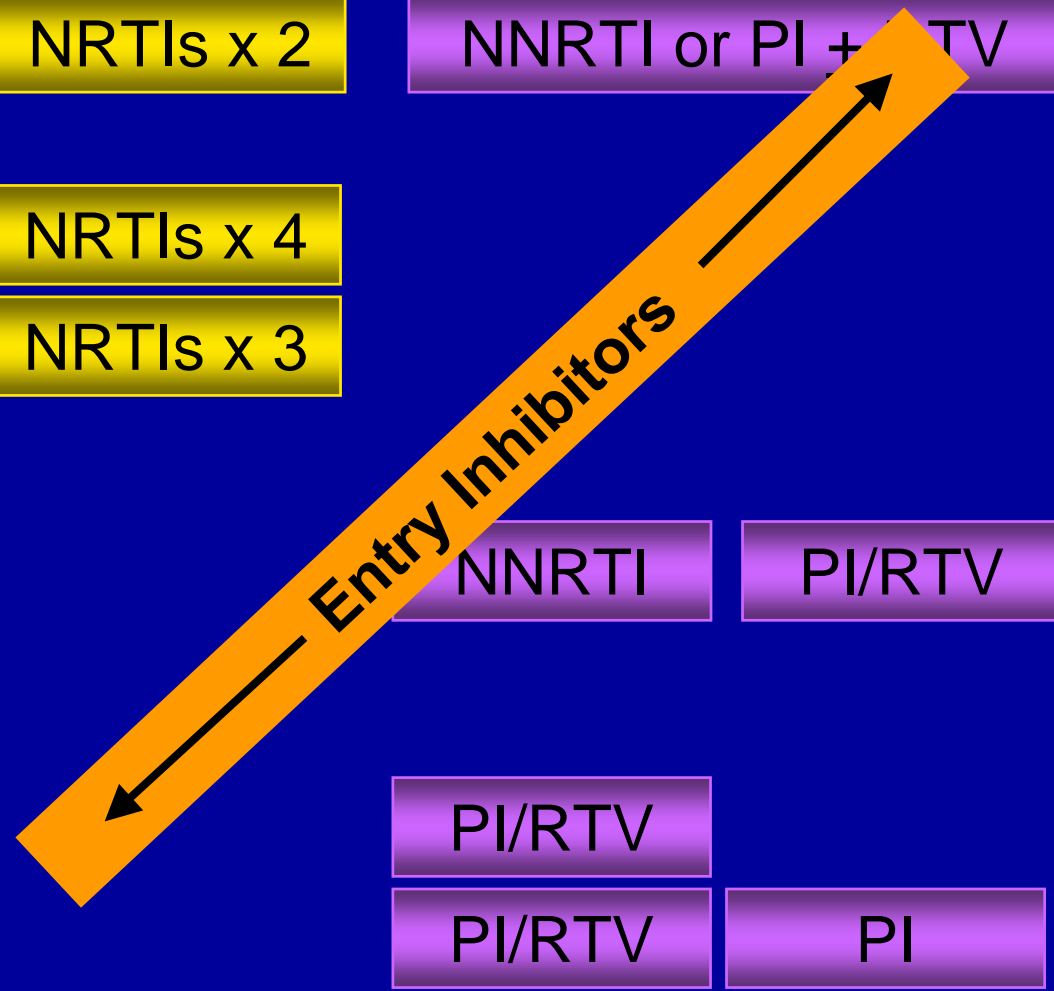
PI/RTV

NRTI/NNRTI-sparing

PI/RTV

PI/RTV

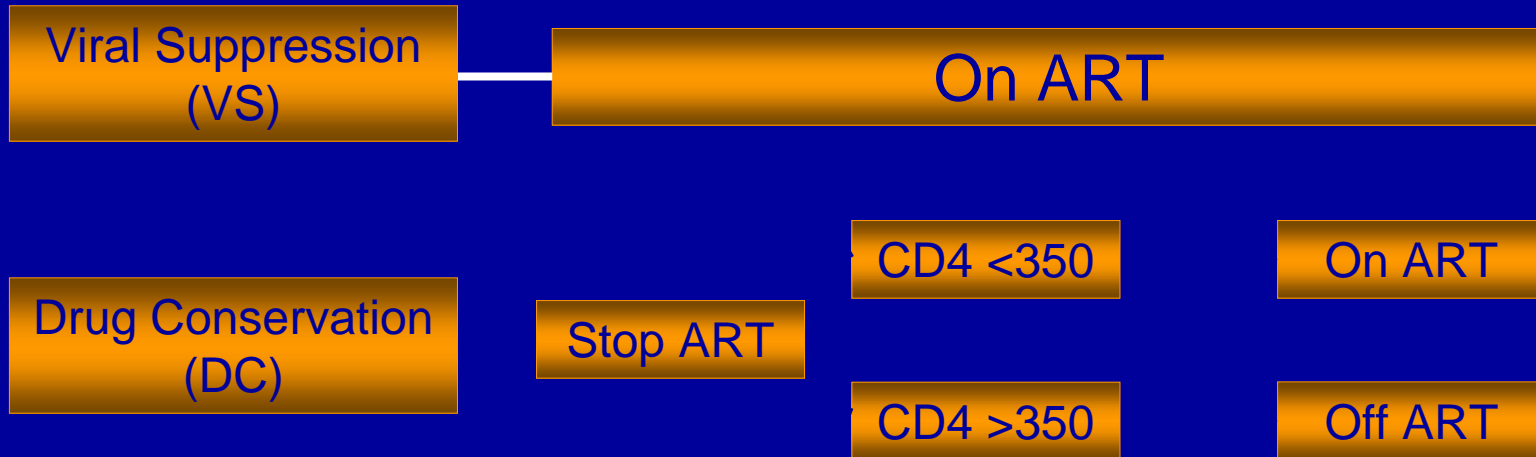
PI



CD4-Guided Treatment CPCRA 065- SMART

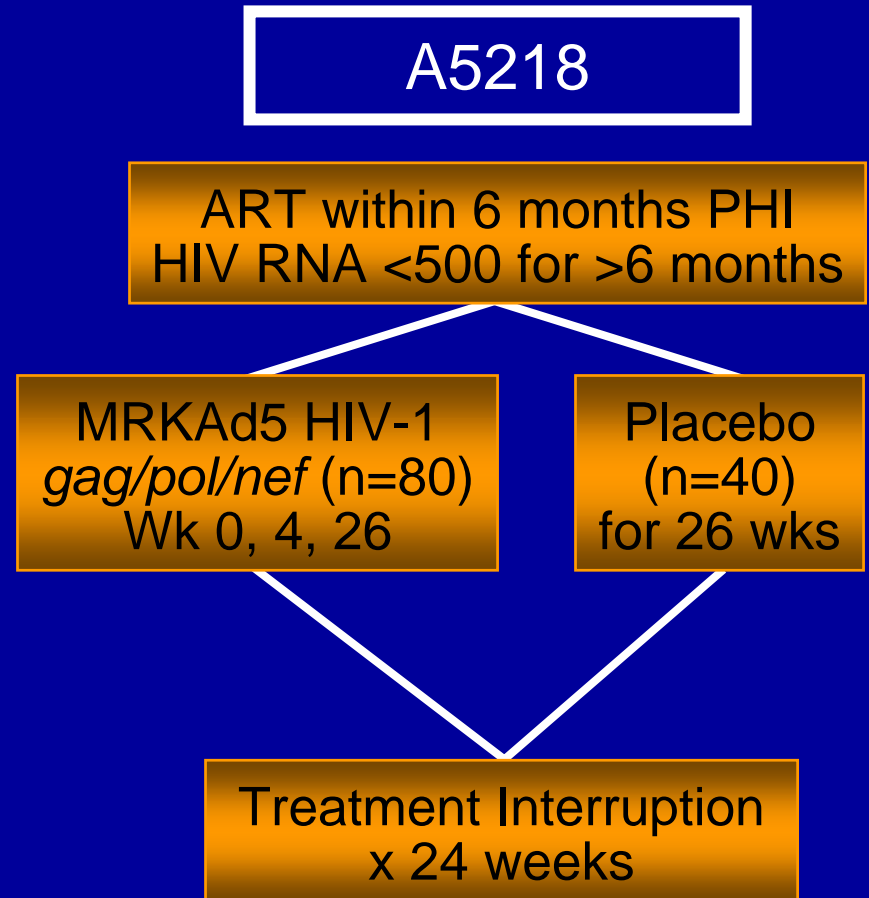
AIDS or Death: ~7 years follow-up (2011)

CD4 > 350 cells/uL
(n ~ 6000)



Treatment During Primary HIV Infection

- Remaining questions
 - Clinical/immunologic relevance of starting ART within weeks or months
 - Optimal means of stopping ART



Timing of Therapy Relative to Acute Infections

- Early vs delayed ART for acute opportunistic infections (A5164, n=280)
- Early vs delayed ART for tuberculosis (A5221, n=800)

TMC125-C223: Study Design

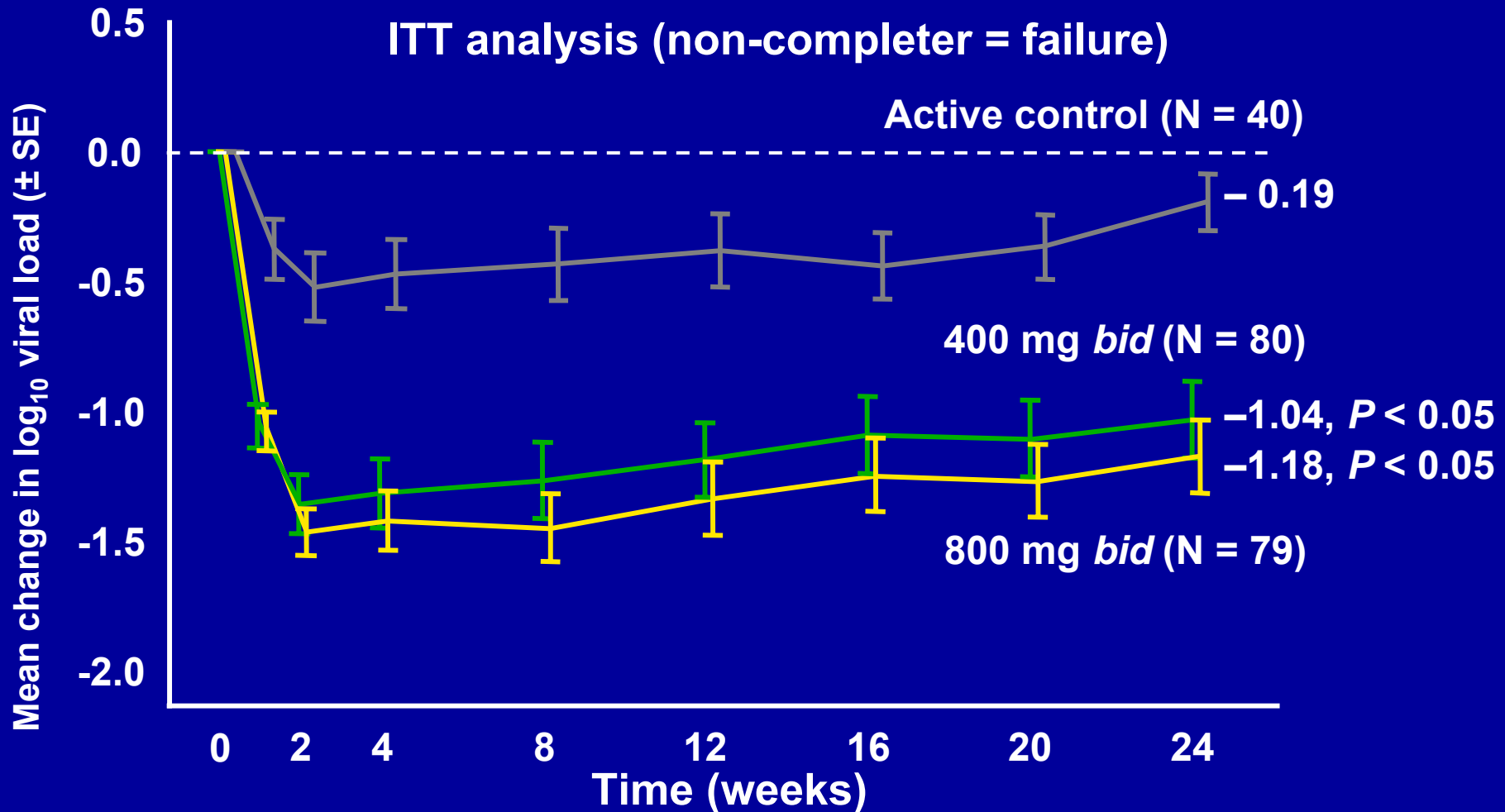


*Active control: best available regimen from licensed agents

†Background regimen: investigator selected NRTIs ± LPV/r ± ENF

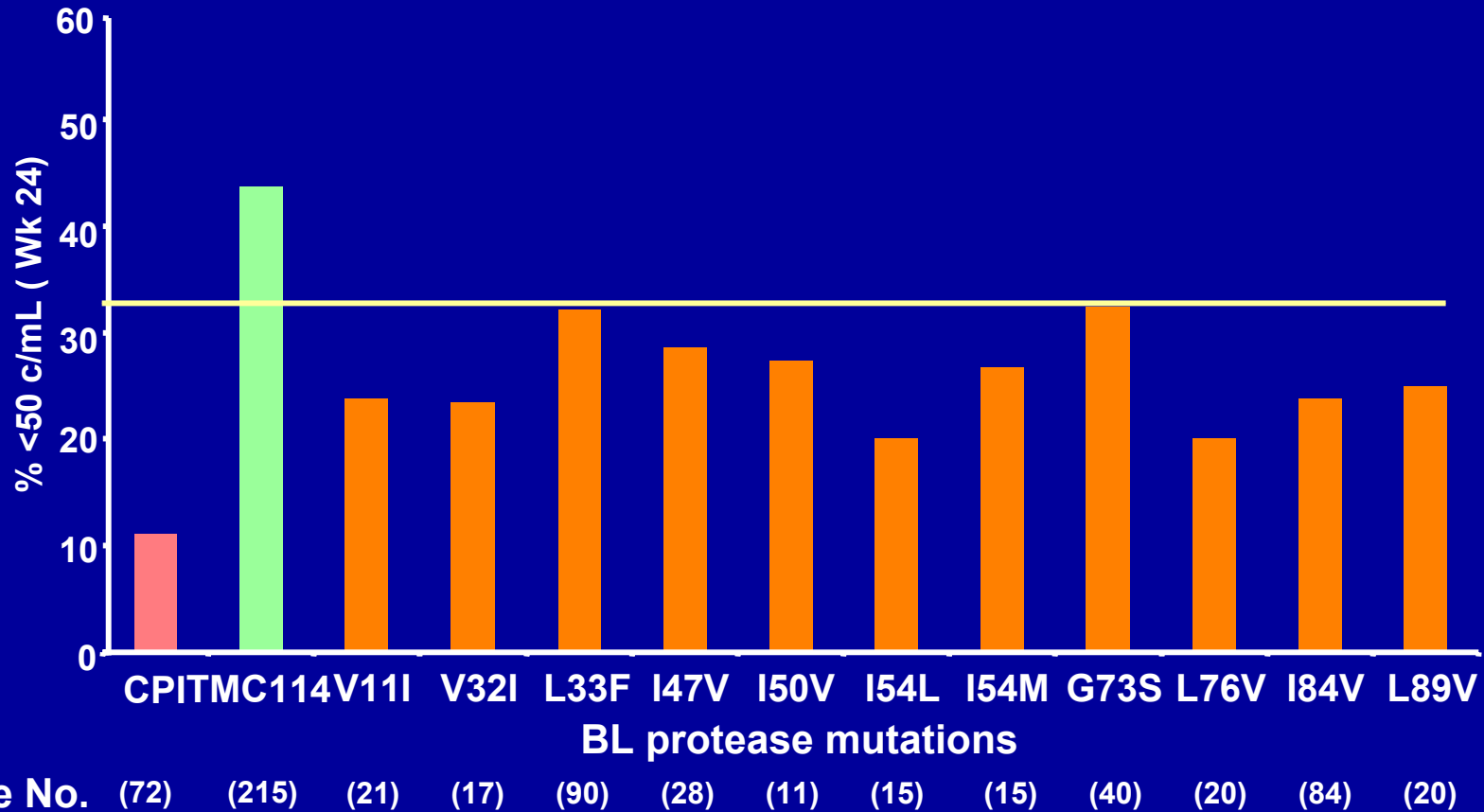
- Documented NNRTI resistance and ≥ 3 primary protease mutations
- Partially blinded, US, randomization 1:2:2
(active control vs 400 mg *bid* vs 800 mg *bid*)
- Viral load $>1,000$ copies/ml

Change in viral load at 24 weeks



p values versus active control

TMC 114: Response (%<50 c/mL) by baseline protease mutations



TMC 114 plus TMC 125: Pilot data in 3 and 4 class ARV experienced patients

- N= 10 on novel combination of 114 / 125 + OB
- PK: No impact on 114/r levels; modest reduction on 125 levels
- Week 12: Median -2.76 log decline;
 - All > 2 log decline
 - All had VL < 400 c/mL
- Median (range) CD4 increase was 87 (83-171) cells/mm³
- No SAE, lab events
 - Possible drug related AE: mild diarrhea, HA, rash
 - All resolve with continuous dosing.

Adverse Events

Study Cohort	800 mg QD (N = 6)	200 mg BID (N = 6)	400 mg BID (N = 6)	800 mg BID (N = 6)	50 mg + RTV QD (N = 6)	Placebo (N = 10)
No. w/ drug-related AEs	2	4	2	1	1	5

- **Drug-related AEs experienced in > 1 patient on GS-9137**
 - Fatigue: Only AE with frequency greater than placebo
 - Diarrhea, HA, Nausea
- **AE: Mild, resolved on treatment**
- **No serious adverse events**
- **No evidence of QT / QT_c changes**

Laboratory Abnormalities

Study Cohort	800 mg QD (N = 6)	200 mg BID (N = 6)	400 mg BID (N = 6)	800 mg BID (N = 6)	50 mg + RTV QD (N = 6)	Placebo (N = 10)
No. w/ any grade abnormalities	2	3	3	5	4	8
No. grade 3/4	0	0	1	0	1	3

- 400 mg BID: non fasting triglycerides (G3)
- 50 mg + RTV: total amylase (G3)
- Placebo: AST (G3), total amylase (G3), CK (G4)

MK-0518:

Triple-class ARV treatment experience

- **Multi-center, double-blind, randomized**
 - 3 doses of MK-0518 (200, 400, 600mg bid) + optimized background *versus*
 - Placebo + OB
- **Inclusion: VL>5000 copies; CD4 > 50 cells**
- **N= 167; Results for pts. with >16 weeks data**

	200 mg (n=40)	400 mg (n=42)	600 mg (n=42)	Placebo (n=43)
Mean VL	4.6	4.8	4.7	4.7
Mean CD4	244	220	226	283
# (%) on	13 (33%)	16 (38%)	16 (38%)	16 (38%)
PSS 0 to PI	98%	95%	88%	84%

Two New Viruses Found

- NY Times
February 26, 2005
By LAWRENCE K. ALTMAN

BOSTON, Feb. 25 - American scientists said Friday that they had discovered two new human viruses in Africa that belong to the same family, retroviruses, as the virus that causes AIDS.

So far, the scientists said, the new viruses have not been linked to any disease, but they are being monitored out of concern that they or similar retroviruses might conceivably spawn another epidemic.

Primary resistance in ARV-naïve adolescents

- Study of resistance in pts age 12-24 from 15 US cities (n=55)
- HIV-infected w/in 180 days using “detuned” assay
- Genotype (GT) and Phenotype (PT) obtained
- Major mutations defined by IAS-USA Drug Resistance Mutations Group

	Genotype	Phenotype
Overall	18%	22%
NRTI	4%	4%
NNRTI	15%	18%
PI	3.6%	5.5%

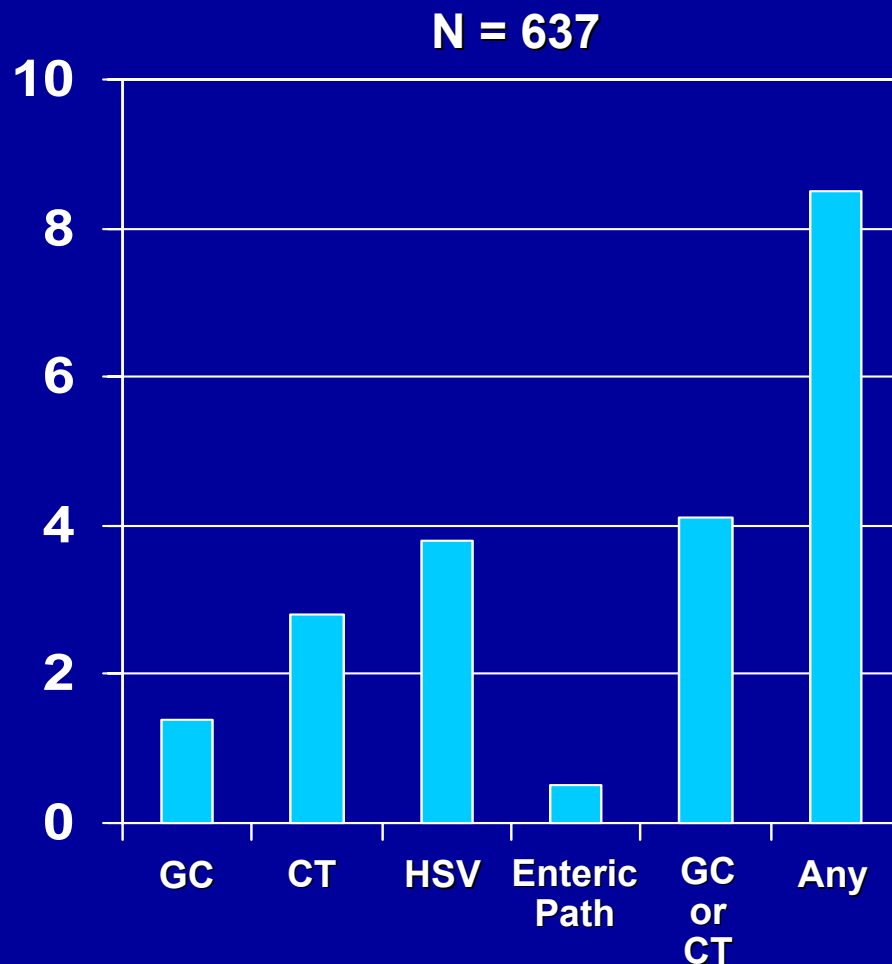
- 1 pt had GT + PT resistance to ARV in all 3 classes

Malignancies in HIV Infection

- CDC: Incidence of malignancy
 - 3 AIDS-defining (AD), 11 non-AD conditions;
 - 1992-2002 in HOPS, ASD
 - N = 59,101 pts; 181,201 person-years follow-up
- Malignancies (RR) significantly higher in HIV+:
 - AD: KS (353.7); NHL (28.7); Cervical (17)
 - Non-AD: Anal (18.3); Hodgkin's (17.5); Liver (4.5); Testicular (3.3); Melanoma (2.1); Oropharyngeal (2); Lung (1.6)
- No increased risk of colorectal, renal CA
- *Decreased* risk of breast and prostate CA
- Conclusion: Promote healthy lifestyle, HAART, screening

Performance of Anal Dysplasia Screening

- **Anal Dysplasia Screening (ADS) begun in 2002**
- **Incidence invasive anal Ca did not decline w/ ADS**
 - % requiring chemo / radiation declined from 92.3% to 72.2% (p=0.36)
- **Unsatisfactory cytology rate 0-62% (14 providers)**
 - No correlation w/ # submitted
- **Cyto-histological agreement at high resolution anoscopy (HRA) improve with experience**
- **High rate of anal STDs on HRA**



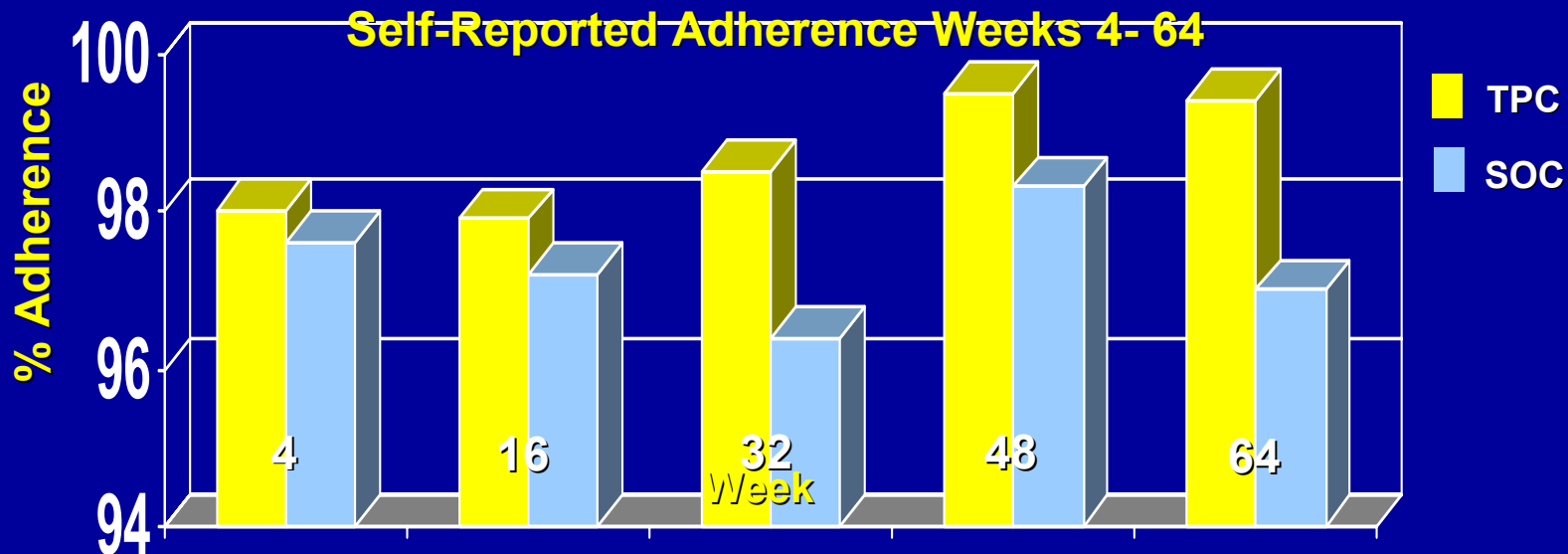
High risk of asymptomatic STDs in HIV+ pts: Four US City Survey

- Prospective study
- N = 264 with asymptomatic STDs:
 - 41 heterosexual men (HSM)
 - 158 MSM
 - 65 women
- Multivariate analysis (OR)
 - All: Age <40 (1.81), Drug use (not marijuana) within 6 mo. (2.76), ≥4 partners in last 6 mo. (4.75)
 - Men: ever sildenafil (2.4), “poppers” in last 6 mo. (4.1), age <36 (3.9)
- STD screening needed;
 - integrate interventions to decrease high risk behavior into routine care

	HSM (%)	MSM (%)	Women (%)
Syphilis	0	5	0
Gonorrhea			
Urine	0	0	0
Rectal	0	3	0
Oropharyngeal	0	4	0
Chlamydia			
Urine	0	2	0
Rectal	0	9	0
Oropharyngeal	2	0	0
Trichomonas	0	0	14

ACTG 731: Adherence Intervention with Proactive Telephone Calls: Pilot Study

- Telephone calls to improve adherence (n=109)
- Randomize: Std. of care (SOC group) vs. SOC + 12 calls (TPC); first 16 weeks of Tx
- Self-reported adherence high in both treatment groups (98%, mean weeks 4-64)
 - 64% “perfect” adherence
- Significantly better adherence was observed in the TPC group (p=0.023)
 - Adherence in TPC group strengthened (p<0.001) in pts with <100% early adherence



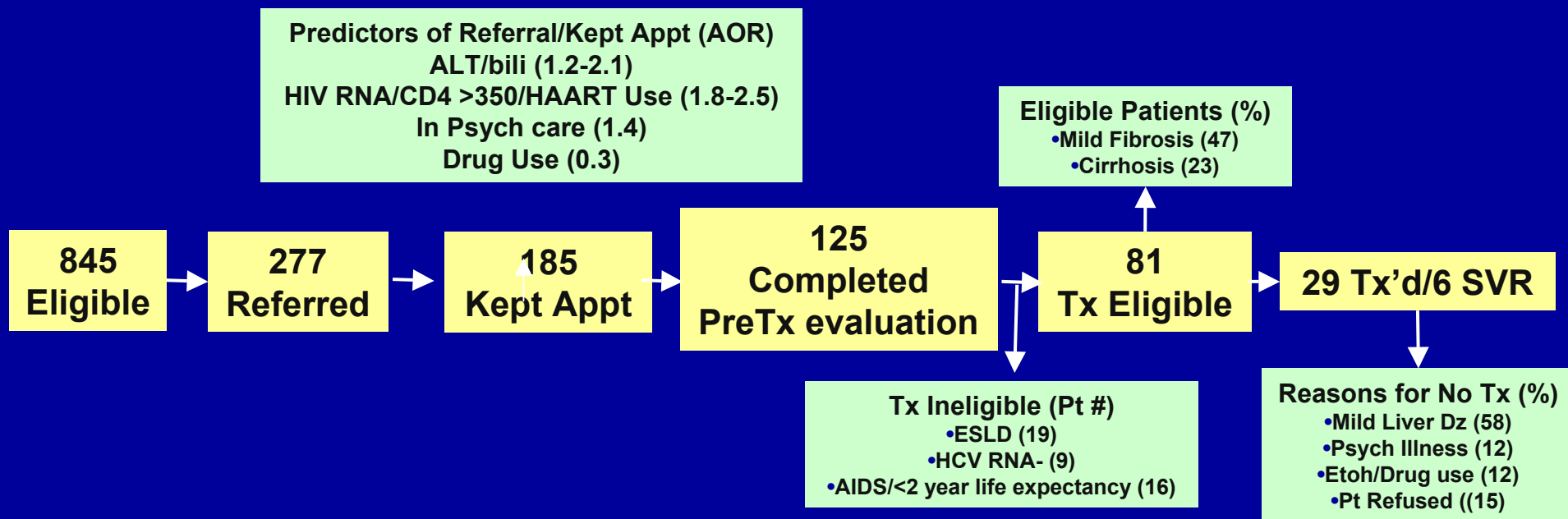
- Multivariate model: Trend for telephone calls to decrease risk of regimen failure
 - HR = .68; p=0.21

Adherence Patterns and Limitations of TDM

- Adherence patterns in Abt. 418 study
 - **ARV naive pts: TDF + FTC + LPV/r BID vs. QD**
- Medication event monitoring system (MEMS) caps:
 - **Track adherence**
 - **Levels of LPV and RTV done @ 3, 8, 16, 24 and 48 weeks**
 - **N =178; 107 QD, 71 BID**
- At 31% of PK visits adherence perfect 1 to 3 days pre PK visit, but <95% during inter-PK intervals
 - **QD 54% vs. BID 84% (p<0.0001)**
- Perfect adherence other than 1-3 days before PK visit:
 - **5% of pts (4% QD vs. 7% BID).**
- Patterns may explain:
 - **Viremia without detectable drug resistance;**
 - **Incomplete virus suppression despite therapeutic drug levels**
- Use of TDM limited by these adherence patterns

Barriers to HCV Treatment

- Johns Hopkins HIV clinic provides care for >3000 pts, ~1/2 are HCV+
- Hepatitis specialty clinic opened in 1998 but to 2003 referral rates poor



- Low referral rates improved (<1% 1998 → 31% 2003);
- Low referral rates (68% w/ CD4 >350 not referred), active drug use remain obstacles to HCV care

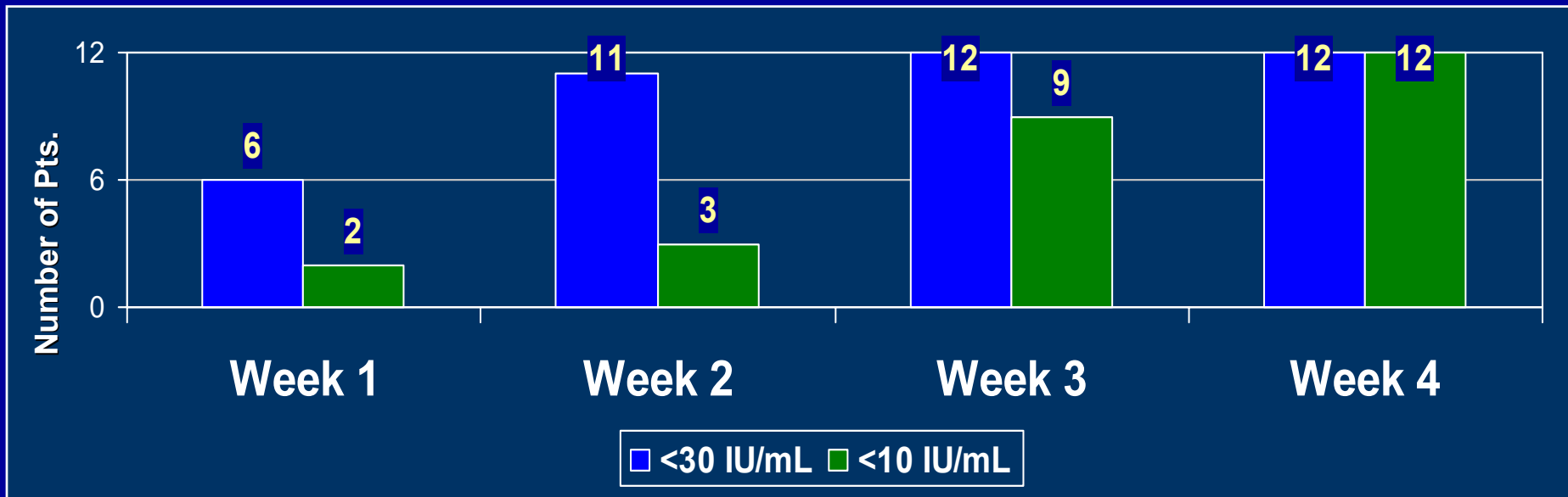
HCV Therapy in HIV/HCV pts: Predictive Value of Week 4 Viral Response

- Predictive value of undetectable HCV RNA (<100 IU/mL)
 - HCV GT 2 or 3
 - 89% also on HAART
- Tx'd for 24 weeks:
 - IFN α -2b + RBV (n = 21)
 - PEG-IFN α -2b + RBV (n=21)
- Overall SVR (ITT): PEG-IFN 71% vs. IFN 43% (p=0.06)
- Relapse rates predicted by HCV RNA at week 4

HCV RNA at Wk 4	N (%)	ETR %	SVR %	Relapse Ratio %
<100 IU/mL	20 (55.6)	95	90	5.3
>100 IU/mL	16 (44.4)	68.7	37.5	45.5

VX-950: HCV Protease Inhibitor

- 28-day, Phase II clinical study
- $n = 12$ Tx-naive patients; HCV GT1; usual BL plasma HCV RNA viremia
- VX-950 750 mg q8h x 28 days; also with PEG-IFN alfa-2a and RBV
 - **After 28 days VX-950 →Tx w/ PEG-IFN and RBV**
- No Tx discontinuations, serious AE



Other Interfering Entities....

- Chronic Substance Abuse
 - Very similar to HIV
 - Chronic, failure to seek early care
 - Best practices
 - Risk reduction to dec transmission (safe sex)
 - TB screening before immune compromised
 - Vaccinations
 - Prophylaxis
 - Subutex

And.....

- Inc cancers
 - Lung, colon
 - Lymphoma
 - Hepatocellular carcinoma
 - Complacency in general population
 - Increase STD
 - Gonorrhea and syphilis
 - Rectal warts





Summary and Conclusions

- The practice of HIV medicine is certain to be shaped by studies underway or in development
- Current treatment paradigms will be enhanced by the availability new formulations of existing agents and studies that define the optimal way to use these drugs
- New treatment paradigms may emerge from studies exploring new strategies to preserve drug classes, minimize time on therapy and to optimally use novel agents and immune-based therapeutics that are in development
- Treatments will also be affected by the management of co morbidities and availability of social changes such as housing, insurance availability and medical care