Rally for Raltegravir in HIV-Treatment-Naïve Patients

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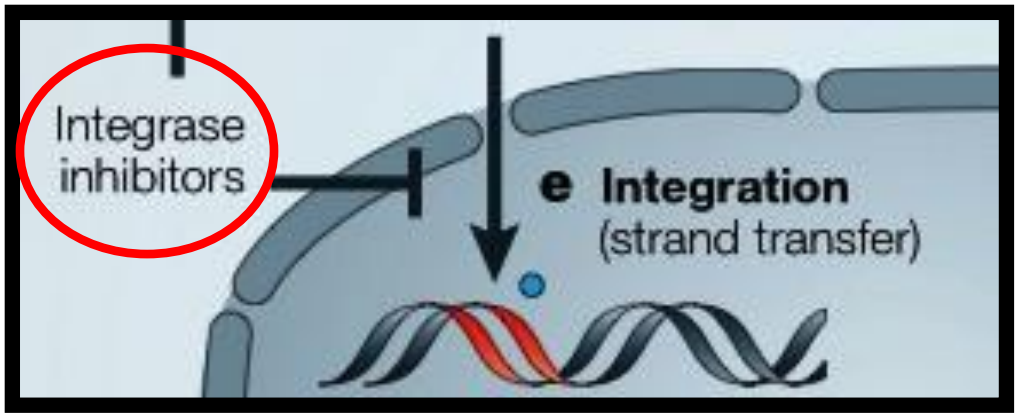


Source: http://www.nature.com/nrd/journal/v1/n1/full/nrd703.html

Objectives

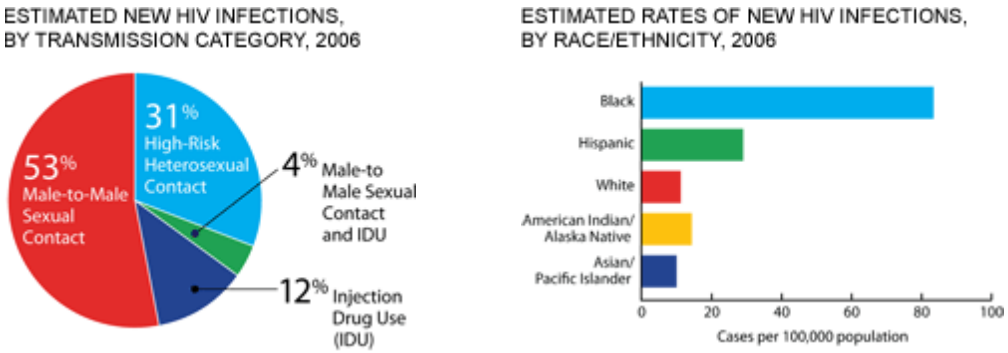
1. Explain the life cycle of HIV, identify drug targets, and understand how drugs work at each target
2. Identify monitoring parameters and clinical importance of adverse effects associated with raltegravir
3. Discuss pros and cons of raltegravir use as part of a first line HAART regimen in treatment naïve HIV patients
4. Describe raltegravir's optimal place in HIV therapy
5. Be familiar with new integrase inhibitors and how they compare to raltegravir

I. Epidemiology

A. National Prevalence/Incidence

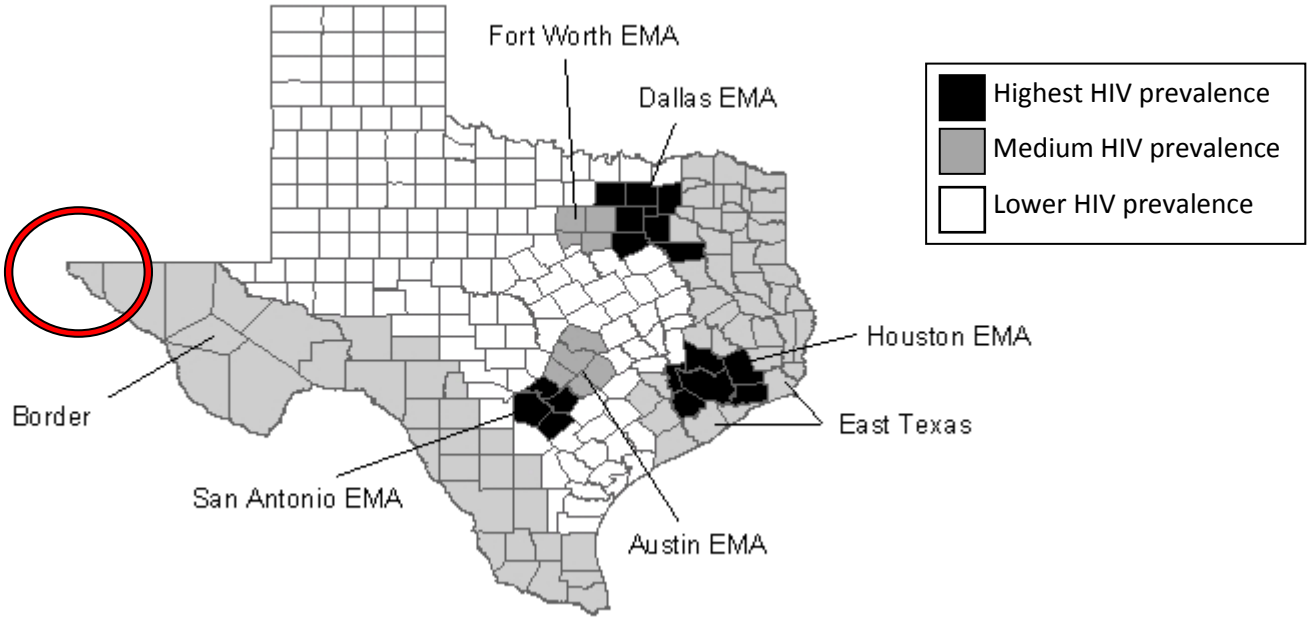
Prevalence: There are currently 1.1 million people infected with HIV in the United States[1]

Incidence:[2]



Source: http://www.cdc.gov/hiv/topics/surveillance/incidence.htm

B. Texas Prevalence[3]



Source: http://www.dshs.state.tx.us/hivstd/reports/HIVandAIDSinTexas.pdf

C. El Paso Incidence[4]

- September 2010: 7 new cases, 72 cases (year-to-date)

II. HIV Infection Process

A. Diagnosis[5]

- Enzyme immunoassay (EIA or ELISA)
  - Uses blood, urine, or oral fluid to detect HIV antibodies (not actual HIV RNA)
- Follow up all (+) EIA results with Western Blot
  - Detects viral proteins

B. Course of HIV Infection[6]

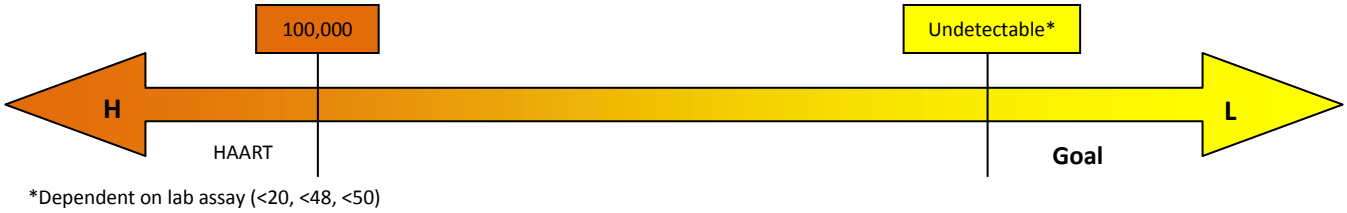
- RNA virus attacks immune system
  - T-Cells, macrophages with CD4 receptors used for viral replication
- Uses CD4 cells for replication and release of new virus into blood stream
- Some CD4 cells are dormant in the G_0 resting phase[7] **(See Appendix B)**

C. HIV Life Cycle and HAART Drugs **(See Appendix C,D)**[8]

1. ***Fusion*** of HIV to CD4 cell: need receptors to attach	Fusion/entry inhibitors
2. ***Uncoating*** of viral proteins/shell	CCR5/entry inhibitors
3. ***Reverse*** *transcription* from RNA→DNA	NRTIs/NNRTIs
4. ***Integration*** DNA→cell nucleus for transcription/translation	Integrase inhibitors
5. ***Processing/***packaging by protease enzyme	Protease Inhibitors
6. Assembly, budding: newly made virus released	Currently not drug target

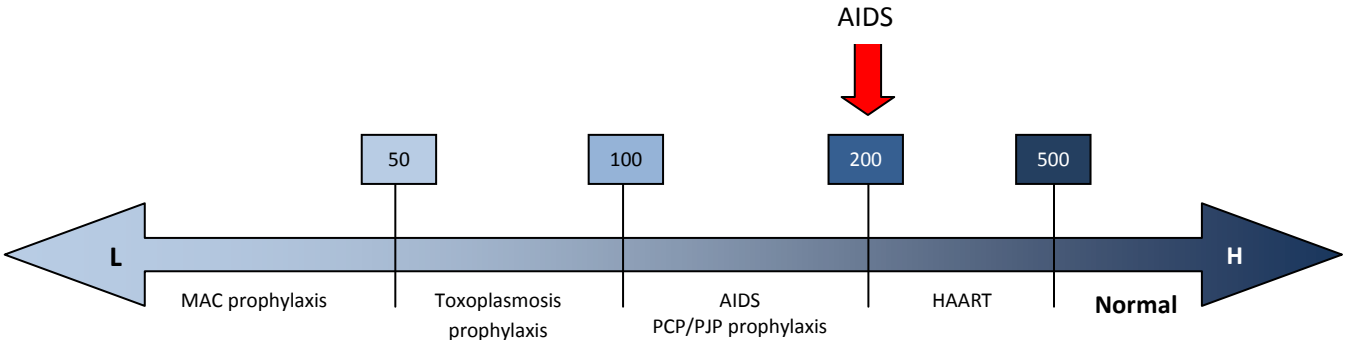
D. HIV-Specific Lab Values[9]

Viral load (HIV RNA copies/mL)



*Dependent on lab assay (<20, <48, <50)

CD4 Count (cells/*u*L)



E. As viral quantity (viral load) increases and CD4 cell count decreases, patient is at risk for opportunistic infections

- *Mycobacterium avium* complex (MAC), cytomegalovirus (CMV), *Pneumocystis jiroveci* pneumonia (PJP/PCP)
- Infections can lead to death

F. Recommendations for Initiating HAART in Treatment-Naïve Adults with HIV Infection[9]

Recommendations for Initiation of HAART in Treatment-Naïve Adults with HIV Infection	
Measure	**Recommendation**
Asymptomatic, CD4≤500 *u*L Viral load >100,000 copies/mL Pregnancy Active hepatitis coinfection Symptomatic HIV Rapid decline in CD4 (>100 *u*L per year) HIV associated nephropathy (HIVAN) High risk for secondary HIV transmission	HAART recommended
Asymptomatic, CD4>500	Consider HAART

G. HAART for treatment naïve patients (**See Appendix E**)[9]

2 NRTI backbone (**tenofovir** + **emtricitabine**)

+

1 other agent from different class (Drug of Choice)

- NNRTI (**efavirenz**)
- PI (**darunavir/ritonavir**)
- PI (**atazanavir/ritonavir**)
- Integrase inhibitor (**raltegravir**)

H. Treatment Goals:[9]

- Viral load undetectable by 6 months of therapy
- CD4 increase of 50-150 cells/*u*L per year

I. Treatment Failure:[9]

- Viral load still detectable by 6 months

J. Resistance:[9]

- Resistance testing:
  - Genotype: Genetic makeup of virus to identify mutations
  - Phenotype: Expression of genes describes actual resistance

Low Genetic Barrier to Resistance		
Drug	**Class**	**Resistance Genes**
Efavirenz	NNRTI	103
Emtricitabine	NRTI	184, 65, 70
Lamivudine	NRTI	184, 65
Nelfinavir	PI	30, 90
Raltegravir	INSTI	143, 148, 155

III. Key Considerations with Raltegravir (Isentress®)[10, 11, 12, 13]

A. Indication

- HIV Infection
  - Salvage therapy (2007)—represents most common place used in therapy currently
  - Initial treatment for HAART-naïve patients (2009)
- Route of Admin: Oral - 400 mg BID (800 mg BID if concurrent rifampin)

B. Clinical Pharmacology

- Mechanism of Action: inhibits HIV integrase, preventing viral DNA insertion into host cell DNA

C. Resistance
- Raltegravir resistance genes 143, 148, 155
- Low barrier to resistance: only 1 mutation needed
- Cross resistant within the integrase inhibitor class
- Not cross resistant with other classes

D. Pharmacokinetics
- Metabolism: Glucuronidation in the liver via GDP, no CYP450
- Elimination: Excretion: Feces 51%, urine 32% (9% unchanged)

E. Tolerability/Safety
- Well tolerated
- No adjustments necessary for renal or hepatic insufficiency
- Drug-drug interactions
    - No effect on P450 system; not likely to interact with drugs by that mechanism
    - Rifampin induces glucuronidation→decreased raltegravir concentrations (increase to 800 mg BID)
        - No interaction with rifabutin – commonly used in HIV/TB co-infection
    - Atazanavir inhibits glucuronidation→increased raltegravir concentrations (no dose adjustment)

IV. Research

A. Raltegravir for treatment experienced patients
- ANRS-139 TRIO[14]
- BENCHMRK[15]

B. Raltegravir for treatment naïve patients
- Protocol 004[16]
- STARTMRK[17]

V. Raltegravir in Salvage Therapy

A. ANRS 139 TRIO trial[14]

High Rate of Virologic Suppression with Raltegravir plus Etravirine and Darunavir/Ritonavir among Treatment-Experienced Patients Infected with Multidrug-Resistant HIV: Results of the ANRS 139 TRIO Trial **Yazdanpanah Y; Fagard C, Descamps D; Taburet AM, Colin C, Roquebert B. et al. CID. 2009;49:1441-9.**	
Objective	Safety and efficacy of raltegravir (INSTI) + etravirine (NNRTI) + darunavir/ritonavir (PI) regimen in treatment-experienced patients with multidrug-resistant HIV infection
Design	Phase II, 103 patients at 49 clinics in France, non-comparative
Patient Population	Inclusion: 103 patients, viral load >1000 copies/mL, history of viralogic failure on NNRTI, other class resistance mutations noted, naïve to study drugs Exclusion: current AIDS-defining infection, organ insufficiency/failure, anemia, pregnant/breastfeeding
Endpoint	Primary: Proportion of patients with viral load <50 copies/mL at 24 weeks (6 months) Secondary: Proportion of patients with viral load <50 copies/mL at 48 weeks (1 yr) Change in viral load and CD4 cell levels from baseline through week 48
Intervention	**Raltegravir** 400 mg BID + **etravirine** two 100 mg tabs BID + **darunavir/ritonavir** 600/100mg BID Physicians could also use optimal backbone therapy (OBT) with NRTIs and/or enfuvirtide in addition
Methods	• Viral load, CD4 levels evaluated at screening, enrollment, weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48 • Genotyped protease, reverse transcriptase genes to determine sensitivity of OBT regimens • Safety: physical exam, blood, urine tests throughout study (independent safety monitoring) • Statistics: intention to treat analysis (treated missed appointments as treatment failures), evaluated association between study regimen and each adverse event, graded severity of ADEs
Results	Baseline data: Demographics matched patterns of HIV infections, mean age 45 years 43% patients had hx AIDS defining event Mean HAART duration before study 13 years, mean CD4 255 cells/*u*L, VL 42,000, Treatment: 84% patients received OBT, 12% received enfuvirtide regimens, 4% no OBT only study meds Viral load: Week 24: 90% patients had <50 copies/mL (50% <50 by 1 month, 88% <50 by 3 months CD4: mean increase in CD4 by week 48 was 108 cells/*u*L (guidelines 50-150 cell/*u*L increase) Adverse effects: Skin rashes, increases in CK (10%) but asymptomatic, no need to discontinue regimen
Authors' Conclusion	• Raltegravir + etravirine + darunavir/ritonavir is viable option for treatment of multi-drug resistant HIV • Efficacy of this regimen is similar to that of therapy in a treatment naïve patient • Regimen was well tolerated • Rapid decline in VL
Comments	• First study that looked at adding 3 active drugs to salvage therapy, rather than 1 possible synergy • No reports on adherence to medications • ADEs related to specific drugs difficult because no control arm (i.e., etravirine→rash in other studies) • No baseline racial or ethnicity data

B. **BENCHMRK trial**[15]

Long-Term Efficacy and Safety of Raltegravir Combined with Optimized Background Therapy in Treatment Experienced Patients with Drug-Resistant HIV Infection: Week 96 Results of the BENCHMRK 1 and 2 Phase III Trials. Steigbigel RT, Cooper DA, Teppler H, Eron JJ, Gatell JM, Kumar PN, et al. CID 2010;50:605-12.	
Objective	Evaluate safety and efficacy of raltegravir vs. placebo in combo with optimized backbone therapy (OBT), in patients with HIV-1 that has triple-class drug resistance and antiretroviral therapy failure
Design	Double-blinded, randomized, placebo controlled, phase III trial in Europe, Asia, Peru, Australia, Americas
Patient Population	• Inclusion: ≥16 years old, HIV RNA >1000 copies/mL while on ART, documented resistance to at least 1 drug in each class • Exclusion: renal insufficiency (SCr >2x ULN), chronic hepatitis, uncontrolled substance abuse, pregnancy, HepB/C only allowed if liver enzymes <5x ULN, cancer on chemotherapy
Endpoints	VL <50 copies/mL; VL <400 copies/mL; change in VL, change in CD4 count from baseline
Intervention	OBT plus either Raltegravir 400 mg BID or placebo in 2:1 ratio

Methods	• Investigator chose OBT based on resistance testing at baseline and patient related factors
	• Clinical visits at regularly scheduled intervals, VL drawn in central lab
	• Virologic failure:
	  ○ HIV RNA >400 or if HIV RNA not reduced by at least 1-$\log_{10}$ by 16 wks (changed to >50 copies/mL
	  ○ HIV RNA level >50 copies/mL by 48 wks
	• After failure pts could either stay in blinded study, unblinded with raltegravir, or drop out of study
	• ADEs rated as definitely, probably, possibly related to drug, staged according to severity

Results	Baseline: primarily white men with AIDS who had been heavily treated with a variety of HAART regimens
	Early data:
	• Efficacy: wk 16 VL <50 61.8% in raltegravir group vs. 34.7% in placebo group (p<0.001)
	wk 48 62.1% vs. 32.9% (p<0.001)
	• Safety:
	  ○ Cancer: 3.5% raltegravir group vs. 1.7% placebo group (no p value provided)
	  ▪ 3 follow up studies found no statistical difference, and may be related to IRIS
	  ○ IRIS:* 3 raltegravir patients (presented as cancers, average CD4 increase 50 cells/*u*L by ~2 months)
	  ○ All other ADE rates similar between groups
	96 wk data:
	• Efficacy:
	  ○ VL<50: 57% raltegravir group vs. 26% placebo group (p<0.001)
	  ○ VL<400: 61% raltegravir group vs. 28% placebo group (p<0.001)
	  ○ CD4 mean increase from baseline: 123 cells/*u*L raltegravir group vs. 49 cells/*u*L placebo (p<0.001)
	  ○ VL mean decrease from baseline: -1.5 $\log_{10}$ vs. -0.6 $\log^{10}$ (p<0.001)
	  ○ 33% of patients failed in raltegravir arm vs. 62% in placebo arm (no p value provided)
	• Safety:
	  ○ ADE rates were similar between two arms; no incidence of IRIS

Authors' Conclusion	Raltegravir is a viable option as it displayed efficacy and tolerability compared with placebo even in population where 90% had history of AIDS and low CD4 counts
Comments	• Adherence not assessed, so hard to know cause of virological failure • Largest double blind placebo controlled trial of raltegravir in multi-drug resistance patients • No p-values given for ADE/discontinuation charts, hard to know relevance of this data

Immune Reconstitution Inflammatory Syndrome (IRIS)[18]

- Paradoxical reaction of the immune system after administration of potent HAART
- Patients present with acute symptoms of previous or dormant infection
  - Treatment: Supportive, antimicrobials for infection, consider corticosteroids although no guidelines yet

VI. Raltegravir in Treatment Naïve Patients

A. Protocol 004 study[16]

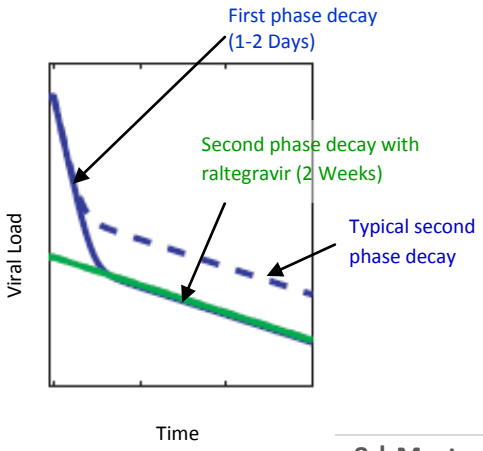
Antiretroviral Therapy with the Intregrase Inhibitor Raltegravir Alters Decay Kinetics of HIV, Significantly Reducing the Second Phase. Protocol 004. Murray JM, Emery S, Kelleher AD, Law M, Chen J, Hazuda DJ, et al. AIDS 2007. 21:2315-21.		
Objective	To investigate effects on viral dynamics* in integrase inhibitors relative to current antiretroviral drugs	
Design	Phase II study, used mathematical models to describe viral dynamics Part 1: compared raltegravir monotherapy of different doses to placebo x10 days Part 2: 48 wks of therapy randomized to **tenofovir/lamivudine** + either **raltegravir** or **efavirenz**	
Patient Population	Inclusion: ≥18 years of age, HAART naïve, viral load ≥5000 copies/mL, CD4 ≥100 cells/*u*L Exclusion: None listed	
Endpoints	Part 1: Viral load for 10 days	Part 2: Viral load, CD4 count at day 15, 57, throughout rest of study until 48 wks
Intervention	Part 1: raltegravir monotherapy with 100mg, 200mg, 400mg, or 600mg BID OR placebo for 10 days (8 patients in each group)	Part 2: **tenofovir** 300 mg**/lamivudine** 300 mg (NRTI) **+ raltegravir** (one of the 4 dosages) or **efavirenz** 600 mg for 48 weeks
Methods	Part 1: First phase decay mathematical models based on measured VL data for 10 days	Part 2: Measured VL at 15, 57 days and through 48 weeks total. Used linear regression to construct decay hypotheses
Results	Part 1: No significant difference among raltegravir doses in VL lowering All doses averaged a 2.2 $\log_{10}$ decrease in VL	Part 2: Day 15 to 168 raltegravir patients significantly more likely to have VL<50 *(decline is faster with raltegravir)* VL 70% lower in second-phase decay in raltegravir group than efavirenz; rate of decline did not differ *(decay began at lower VL in raltegravir arm)*
Authors' Conclusion	Part 1: raltegravir is potent anti-retroviral drug, all doses showed a rapid decline in VL	Part 2: New hypotheses behind viral decay kinetics: 1) second-phase virus arises from cells newly infected by long-lived infected cells **OR** 2) second-phase virus arises from activation of latent cells with unintegrated HIV DNA • Raltegravir reduces viral production from second-phase by 70% above standard regimens *(raltegravir is working synergistically with OBT)* • Raltegravir extends phase I decay
Comments	• From this study we know raltegravir is potent and rapid acting, effective at treating HAART-naïve pts • Full clearance of virus predicted between 8 and 60 years dependent on residual viral replication • This could mean that over time raltegravir can clear virus reservoirs (unknown significance at this time) • Better to give raltegravir at the beginning of therapy because may prevent reservoirs from being made	

*Decrease in viral load

Phases of Viral Decay[16,19,20, 21]

Phase 1:
- Rapid decline in viral load (t½ decay=1-2 days)
- Clearance of free plasma virus

Phase 2:
- Slower decline in viral load (t½ decay=2 weeks)
- Activation and release of virus from sanctuary sites
- Drugs are then able to target



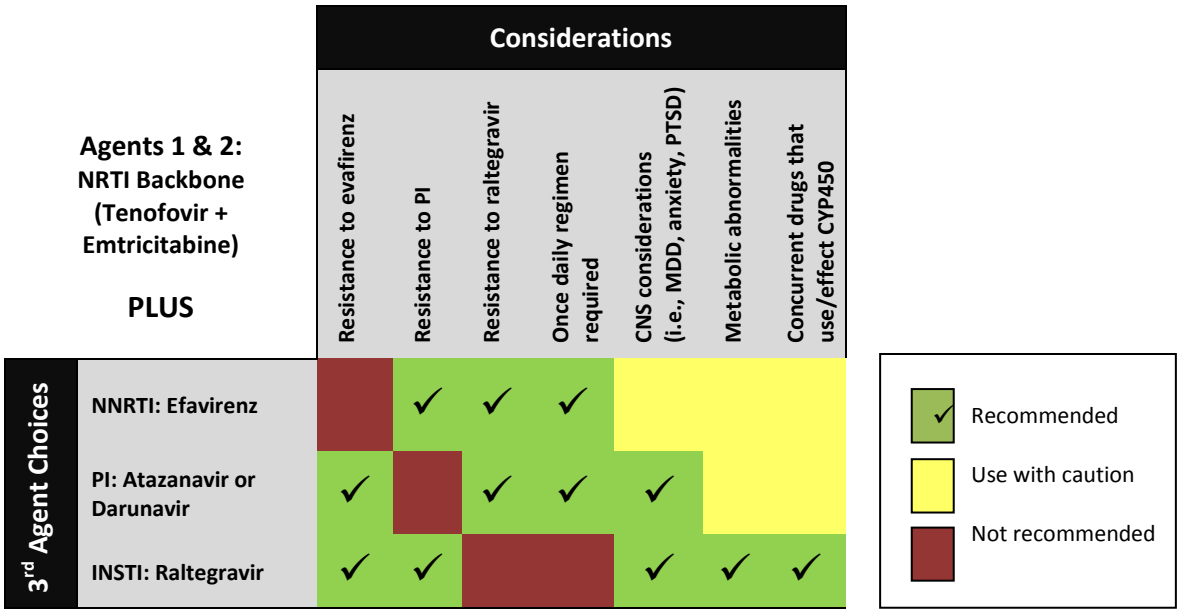
B. **STARTMRK trial**[17]

Safety and effi cacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naïve patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. STARTMRK Trial. Lennox JL, DeJesus E, Lazzanrin A, Pollard RB, Madruga JVR, Berger DS, et al. Lancet 2009;374:796-806.	
Objective	Safety and efficacy of **raltegravir** vs. **efavirenz** as part of combination ART for treatment-naïve patients.
Design	Multi-center, randomized, non-inferiority trial between 9/14/06 and 6/5/08 in 563 tx-naïve patients
Patient Population	Inclusion: HIV-1 infection, viral load >5000 copies/mL, ≥18 yo, HAART naïve Exclusion: Hepatic/renal failure, resistance to study medication at baseline, pregnant/breastfeeding
Endpoints	Primary: achievement of viral load <50 copies/mL at week 48 Secondary: viral load <400 copies/mL, change from baseline CD4 at week 48
Intervention	**Tenofovir** 300 mg/**emtricitabine** 200 mg QDAY + **Raltegravir** 400 mg BID x 48 weeks OR **Tenofovir** 300 mg/**emtricitabine** 200 mg QDAY + **Efavirenz** 600 mg daily x 48 weeks
Methods	• Stratified by presence of concurrent Hepatitis infection and by HIV RNA >50,000 vs. ≤50,000 • Randomized, double blind, 1:1 allocation • Clinical status/labs evaluated at regularly scheduled visits and PRN • Adherence assessed by diary and pill counts • Non-responders: patients with HIV RNA ≥50 at 24 wks • Rebounders: after initial response to HAART, HIV RNA ≥50 x2 consecutive measurements 1 wk apart • ADEs recorded as definitely, probably, or possibly related to drug therapy; mild, moderate, or severe • Statistics: o Kaplan-Meier estimates of primary endpoint o Two-tailed Fisher's exact test for differences in Adverse effect rates between groups o Reported all patients who didn't complete study as treatment failures
Results	Baseline: 35% from Mexico/South America, mean age 38, history AIDS 14%, over 50% had VL ≥100,000 Primary endpoint: • 86.1% pts in raltegravir group, 81.9% pts in efavirenz (p<0.0001) • Time to VL at goal shorter in raltegravir group (p<0.0001) Secondary endpoint: • Mean change in CD4 189 cells/*u*L raltegravir vs. 163 cells/*u*L efavirenz (p=0.0184) • Increase in CD4 was greater in patients with VL <100,000 at baseline (no p value provided) • Proportion of patients who discontinued not different among groups (no p value provided) ADEs: • IRIS in 6% raltegravir patients vs. 4% efavirenz (no p value provided) • CNS effects efavirenz > raltegravir (18% vs. 10%) (p=0.0149) • Increases in lipid panel efavirenz > raltegravir (p<0.0001) o Total cholesterol: 70mg/dL vs. 20mg/dL increase o HDL: 22mg/dL vs. 8.9mg/dL increase o LDL: 34mg/dL vs. 13mg/dL increase o TG: 80mg/dL vs. 6.2mg/dL increase
Authors' Conclusion	• Raltegravir properties: o Efficacy non-inferior to efavirenz therapy o Fewer CNS side effects o Less effect on lipids (no statistical difference in other lab values) o More rapid decrease in viral load and increase in CD4 count
Comments	• Did not stratify IRIS incidence by CD4 count (because IRIS was not expected) • Was not powered to show superiority, only non-inferiority • Strong study design, assessed adherence, blinded well • Due to matched raltegravir tablets, all patients took a tablet BID, unknown effect on compliance

VII. Take Home Points

Advantages of RAL for treatment-naïve patients	Disadvantages of RAL for treatment-naïve patients
Less effect on lipids than protease inhibitors	Lower barrier to resistance
Less effect on CNS than efavirenz	Twice daily dosing, possible adherence issues
Equivalent efficacious compared to efavirenz	IRIS possible with raltegravir due to rapid effects
Rapid decline in viral load, increase in CD4 count (Possible effect in preserving immune system)	
Use in TB patients[23]	
Use in post-transplant patients[23]	
Earlier administration less likely to cause IRIS than salvage therapy? (more studies needed)	

Considerations for Initial Anti-Retroviral Regimen



VIII. Future Integrase Inhibitor[24]

A. Elvitegravir
- Dosed once daily
- Will need boosting agent (already been created and in testing)
- More drug-drug interactions (CYP 450)
- Cross resistance to raltegravir
- Clinical trials currently being done

IX. Summary

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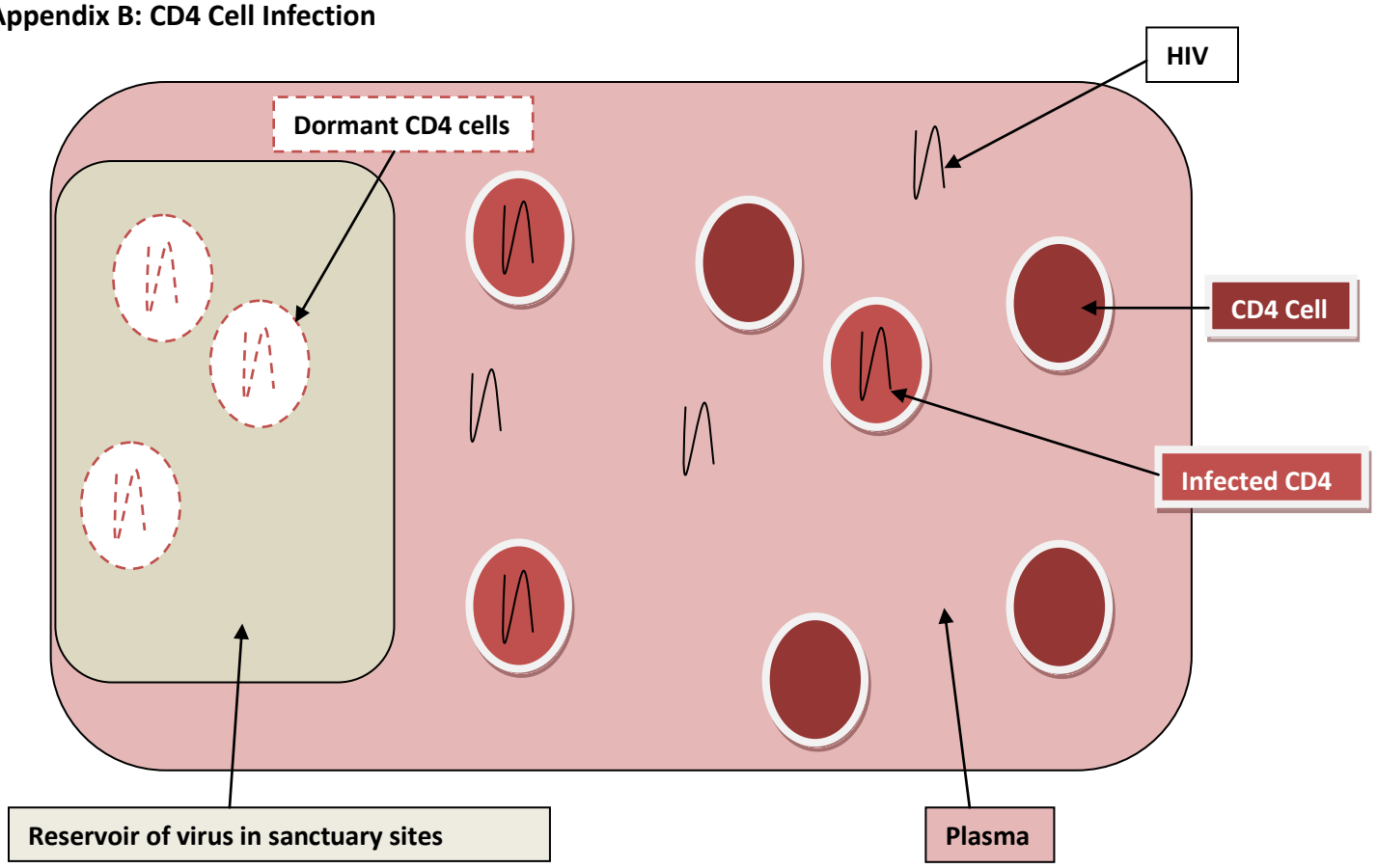
Appendix A: Common HIV-Related Acronyms

AIDS	Auto-immune deficiency syndrome	**MAC**	*Mycobacterium avium-intracellulare*
ART	Anti-retroviral therapy	**MSM**	Men who have sex with men
CCR5	Chemokine Co-Receptor 5	**NNRTI**	Non-nucleoside reverse transcriptase inhibitor
CK/CPK	Creatine Phosphokinase	**NRTI**	Nucleoside reverse transcriptase inhibitor
CMV	Cytomegalovirus	**OBT**	Optimized Background/Backbone Therapy
HAART	Highly Active Anti-Retroviral Therapy	**OI**	Opportunistic infection
HIV	Human immunodeficiency virus	**PI**	Protease inhibitor
INSTI	Integrase strand transfer inhibitor	**PJP/PCP**	*Pneumocystis jiroveci* pneumonia
IRIS	Immune Reconstitution Inflammatory Syndrome	**VL**	Viral load

Appendix B: CD4 Cell Infection



Appendix C: Life Cycle of HIV and Drug Targets

http://www.nature.com/nrd/journal/v1/n1/full/nrd703.html

HIV Virus

1. ***Fusion*** of HIV to CD4 cell: need receptors to attach

Fusion/entry inhibitors

2. ***Uncoating*** of viral proteins/shell

CCR5/entry inhibitors

3. ***Reverse transcription*** from RNA→DNA

NNRTIs/NRTIs

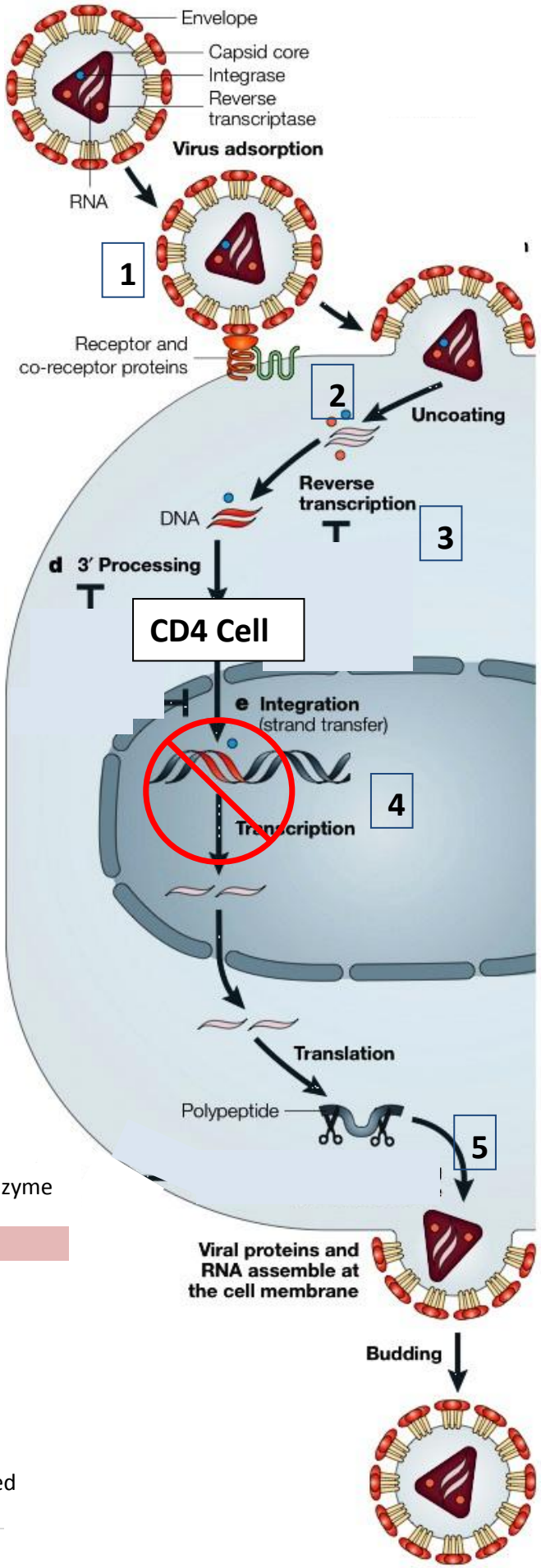
4. ***Integration***: DNA→cell nucleus for transcription/translation

Integrase inhibitors

5. ***Processing***/packaging by protease enzyme

Protease Inhibitors

Assembly, budding: newly made virus released



Appendix D: HAART Drug Review[8]

Class	Generic	Brand	Abbreviation	Side Effects
NRTI	Abacavir	Ziagen®	ABC	Lactic Acidosis Mitochondrial toxicity
	Didanosine	Videx®	ddI	
	Emtricitabine	**Emtriva®**	**FTC**	
	Lamivudine	Epivir®	3TC	
	Stavudine	Zerit®	d4T	
	Tenofovir	**Viread®**	**TDF**	
	Zidovudine	Retrovir®	AZT and ZDV	
NNRTI	Delavirdine	Rescriptor®	DLV	**Efavirenz (CNS effects)** Rash
	Efavirenz	**Sustiva®**	**EFV**	
	Etravirine	Intelence®	ETR	
	Nevirapine	Viramune®	NVP	
PI	**Atazanavir**	**Rayataz®**	**ATV**	**Metabolic: hyperlipidemia, fat redistribution, hyperglycemia, GI related side effects**
	Darunavir	**Prezista®**	**DRV and PRZ**	
	Fosamprenavir	Lexiva®	FPV	
	Indinavir	Crixivan®	IDV	
	Lopinavir/ritonavir	Kaletra®	LPV/RTV	
	Nelfinavir	Viracept®	NFV	
	Ritonavir	Norvir®	RTV	
	Saquinavir	Invirase®	SQV	
	Tipranavir	Aptivus®	TPV	
Fusion/entry inhibitor	Enfuvirtide	Fuzeon®	T-20	Injection site reactions
CCR5/entry inhibitor	Maraviroc	Selzentry®	MVC	Hepatic side effects
Integrase inhibitor	**Raltegravir**	**Isentress®**	**RAL**	**IRIS**

Bold = Component of preferred regimens for treatment-naïve pts

Combination Tablets	
FTC, TDF	**Truvada®**
FTC, TDF, EFV	**Atripla®**
3TC, ABC	Epzicom®
3TC, AZT	Combivir®
3TC, AZT, ABC	Trizivir®

Appendix E: Rationale for Preferred Agents in Treatment-Naïve Patients[9]

Agents	Advantages	Disadvantages
NRTI Backbone		
Recommended		
Tenofovir + emtricitabine	Combo available (Truvada®) Once daily dosing	Emtricitabine: low genetic barrier to resistance Tenofovir: renal dysfunction, bone mineral density precautions
Alternative		
Abacavir + lamivudine	Combination available Once daily dosing	Weaker efficacy in patients >100,000 VL Lamivudine: low genetic barrier to resistance Abacavir: hypersensitivity, CV risk
Key Third Agent		
Recommended		
NNRTI (Efavirenz)	Standard of care Fixed dose combo with tenofovir/emtricitabine Once daily dosing	Contraindicated in pregnancy Caution in major psychiatric illness Low genetic barrier to resistance
PI (Atazanavir/ritonavir)	Once daily dosing Less effects on lipids than lopinavir/ritonavir	Risk of nephrolithiasis Risk of hyperbilirubinemia Interaction with acid reducing agents
PI (Darunavir/ritonavir)	Once daily dosing	Limited experience in treatment-naïve pts
INSTI (Raltegravir)	Low drug interaction potential Rapid decline in VL Rapid increase in CD4	Low genetic barrier to resistance Limited experience in treatment-naïve pts Twice daily dosing
Alternative		
PI (Lopinavir/ritonavir)	Lower pill burden (only PI co-formulated with ritonavir) Can be given once daily in treatment naïve patients	Potential for hyperlipidemia
PI (Fosamprenavir/ritonavir)	Similar to lopinavir/ritonavir	
CCR5 Inhibitor (Maraviroc)		Need viral tropism assay before starting drug Limited experience in treatment naïve pts Maybe more useful in experienced patients

Appendix F: Helpful HIV Websites

Drug Interactions: http://www.hiv-druginteractions.org/
Resistance: http://hivdb.stanford.edu
Guidelines: www.aidsinfo.nih.gov

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