

Antibiotics, Antivirals

Dorothee von Laer
FIRST Catch-up Course: CuC1
Basics in Medicine and Pharmacology
for Scientists

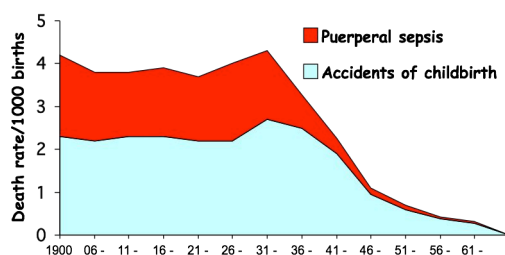
http://www.englischwoerterbuch-medicin.de/index_hxmod_userInput_Erysipel_sprache_de.php

The epidemiologic view: fighting infectious diseases

The greatest impact on infectious diseases was achieved by

- **Separation of drinking water and sewage**
- **Food hygiene (eg pasteurizing milk)**
- **General hygiene (Semmelweis)**
- **Vaccination**
- Patient + carrier isolation
- Reduce shedding from infected: antibiotics

The patient's perspective: Maternal Mortality per 1000 births in England and Wales, 1900 - 1965



Fighting bacteria

- Sterilization: kill/eliminate all bacteria, heat, ethylene oxide, filtration, UV, ionizing radiation
- Disinfectants for instruments (phenol-based)
- Antiseptics for topical use (skin, mucous membranes, eg iodine, 70% alcohol)

Antibiotics

See also:

<http://pathmicro.med.sc.edu/mayer/antibiot.htm>
<http://pathmicro.med.sc.edu/fox/antibiotics1.htm>

Principles and Definitions

- Selectivity
 - Toxic for bacterial cell not for host cell because target exists only in bacteria (cell wall) or bacterial target more sensitive (ribosome)
- Act in conjunction with host immune defense
- Categories of antibiotics
 - Bacteriostatic: stop bacterial replication
 - Duration of treatment sufficient for host defenses
 - Bactericidal: kill bacteria
 - Usually antibiotic of choice

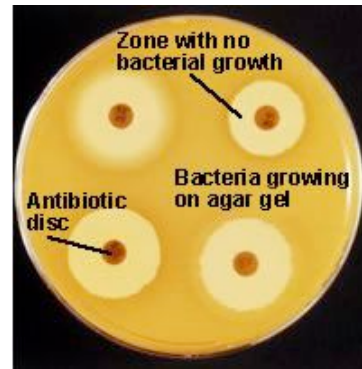
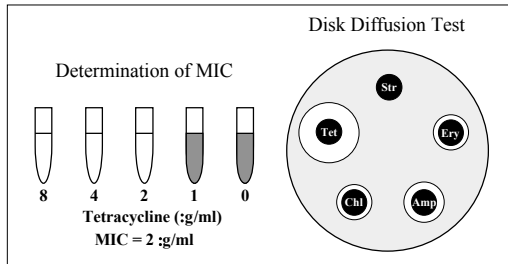
Principles and Definitions

- Selectivity
- Therapeutic index
- Categories of antibiotics
 - Use of bacteriostatic vs bactericidal antibiotic
 - Therapeutic index better for bacteriostatic antibiotic
 - Resistance to bactericidal antibiotic
 - Protein toxin mediates disease – use bacteriostatic protein synthesis inhibitor

Principles and Definitions

- Antibiotic susceptibility testing (in vitro)
 - Minimum inhibitory concentration (MIC)
 - Lowest concentration that results in inhibition of visible growth
 - Minimum bactericidal concentration (MBC)
 - Lowest concentration that kills 99.9% of the original inoculum

Antibiotic Susceptibility Testing



Zone Diameter Standards for Disk Diffusion Tests

Antimicrobial agent (amt. per disk) and organism	Zone diameter (mm)				Approx. MIC (µg/ml) for:	
	R	I	MS	S	R	S
Ampicillin (10 µg)						
<i>Enterobacteriaceae</i>	<11	12-13		>14	>32	<8
<i>Haemophilus</i> spp.	<19			>20	>4	<2
Enterococci	<16		>17		>16	
Tetracycline (30 µg)	<14	15-18		>19	>16	<4

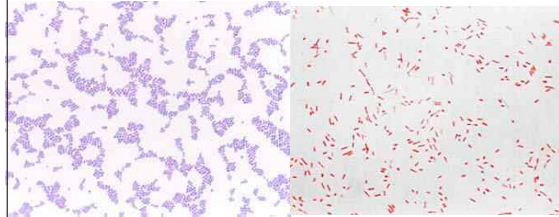
Principles and Definitions

- Combination therapy
 - Prevent emergence of resistant strains
 - Temporary treatment until diagnosis is made
 - Antibiotic synergism
 - Penicillins and aminoglycosides
 - CAUTION: Antibiotic antagonism
 - Penicillins and bacteriostatic antibiotics
- Antibiotics (derived from natural compounds)
- Chemotherapeutic agents (synthetic antimicrobial)
- Antimicrobials (general term)

Inhibitors of cell wall synthesis

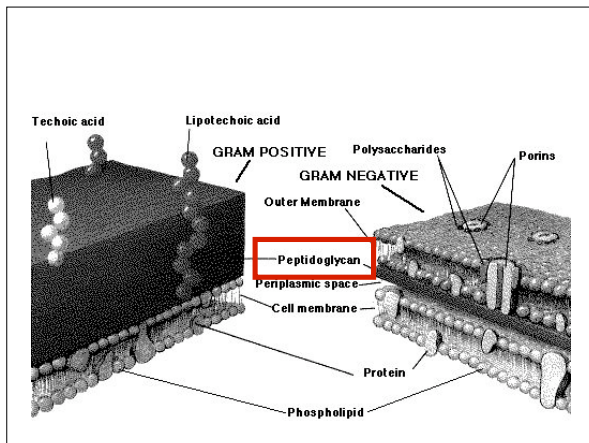
Gram+

Gram-

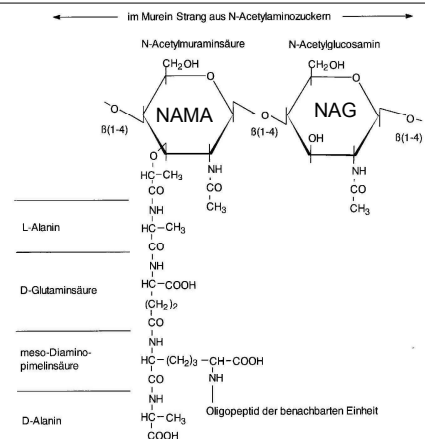


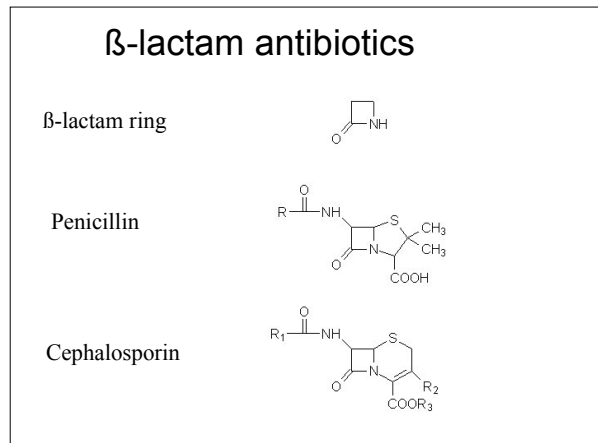
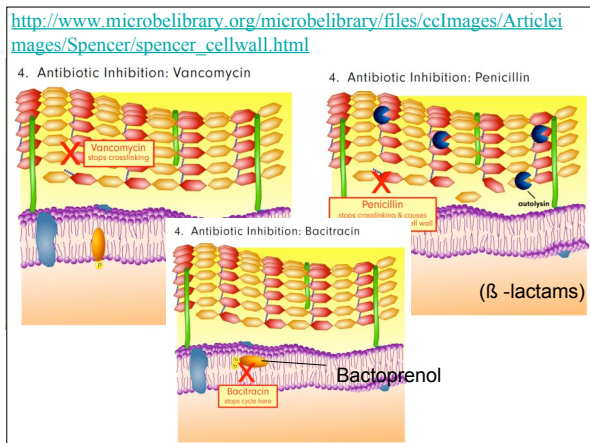
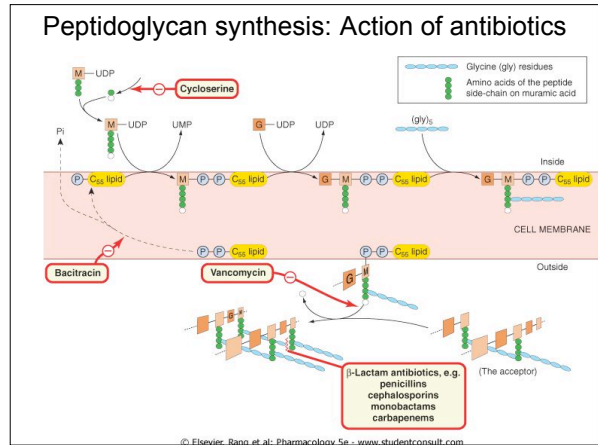
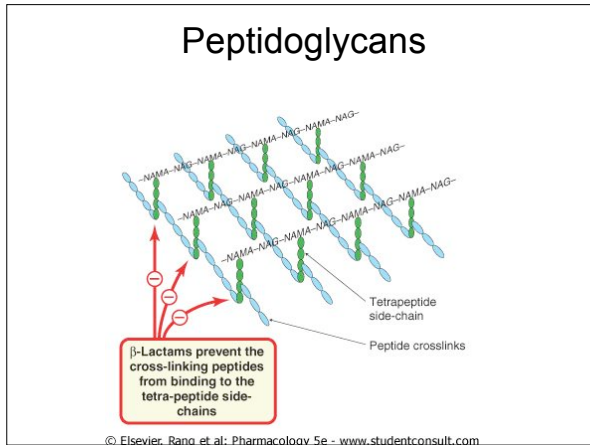
Gram stain:
 gentian violet iodine -> iodine in potassium iodide
 -> ethyl alcohol -> counter stain (red)

Both have a peptidoglycan cell wall but.....



Peptidoglycan (murein)





Penicillins

- Bactericidal
- Inhibit transpeptidation
- Block inhibitor of autolytic enzyme in cell wall (if this enzyme is defective bacteria are susceptible, but Ps. are only bacteriostatic.)
- First P. was Pen. G (not orally bioavailable)
- Do not enter mammalian cells
- BBB penetration only during meningitis
- 90% renal elimination

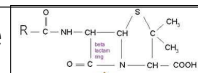
penicillins

- Natural penicillins Mold.
 - About all there was during WWII
 - Then most staph was susceptible to PCN.
 - Now over 90% of the strains are resistant to PCN.
- R1 side chain-modified penicillins:
 - Penicillinase-resistant penicillins
 - Methicillin, Staphcillin, Unapen
 - [MRSA – can live on your hands for three hours]
 - Aminopenicillins
 - Ampicillin, Unasyn (may cause nephritis, agranulocytosis)
 - Extended spectrum penicillins
 - Ticarcillin, Piperacillin

Resistance

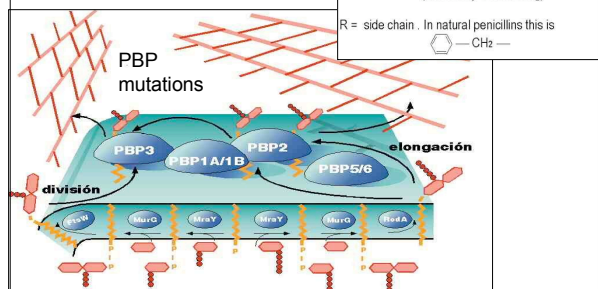
1. β -lactamases on R plasmids
 - Clavulanic acid inhibits β -lactamases, >given in conjunction with β -lactams
2. Mutations of penicillin binding proteins PBP
3. In g-: mutation of outer membrane porins

β -lactam resistance mechanisms



Site of penicillinase action (break in β lactam ring)

R = side chain. In natural penicillins this is c1ccccc1-CH2-



Penicillins: drug of choice for

- Meningitis
- Erysipelas
- Pharyngitis
- Syphilis
- GO
- P. aeruginosa (piperacillin)
- Otitis media, bronchitis, urinary tract (amoxi.)

Penicillins: major unwanted side effects (USE)

- Hypersensitivity!!!!
- Broad spectrum P. disturb gut flora

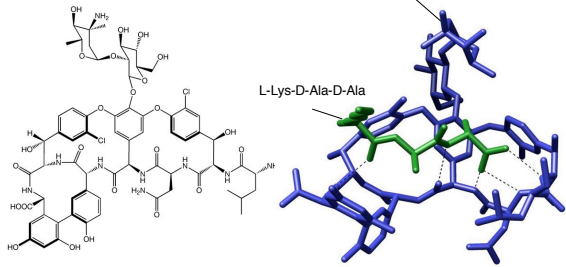
Cephalosporins

- Cephalosporins/Cephamecins/Semisynthetic broad spectrum
- Mechanism of action as penicillins
- Penetrate outer membrane of gram-
- Most are β -lactamase sensitive
- Many cross BBB
- Divided into generation 1 - 4 with increasing spectrum
- A drug of choice for
 - i.v: septicemia, biliary tract infections, meningitis
 - oral: sinusitis, pneumonia.
- Cave hypersensitivity , 10% cross with P.

Vancomycin (glycopeptid)

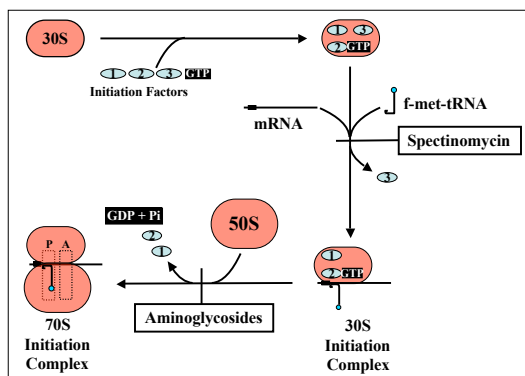
- Used for treating MRSA
- Orally not absorbed (only for C. difficile)
- Blocks cell wall synthesis
- Adverse reactions
 - Hypersensitivity/anaphylaxis
 - "red man syndrome"
 - Neutropenia
 - Hearing loss (temporary/permanent)

Vancomycin

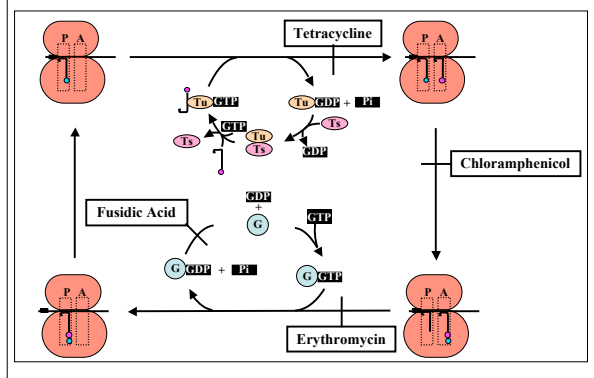


Antibiotics that Inhibit Protein Synthesis

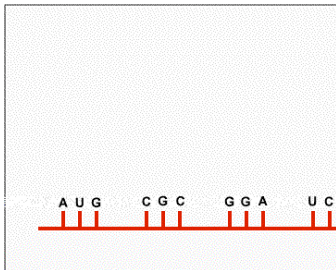
Review of Initiation of Protein Synthesis



Review of Elongation of Protein Synthesis



Protein Synthesis



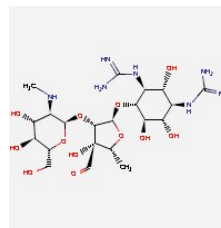
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Protein Synthesis Inhibitors

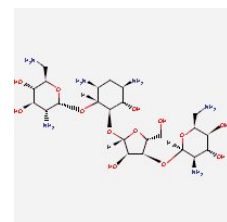
- Mostly bacteriostatic
- Selectivity due to differences in prokaryotic and eukaryotic ribosomes
- Some toxicity - eukaryotic 70S ribosomes

Antimicrobials that Bind to the 30S Ribosomal Subunit

Aminoglycosides (bactericidal)



Streptomycin



Neomycin

Aminoglycosides (bactericidal)

streptomycin, kanamycin, gentamicin, tobramycin, amikacin, netilmicin, neomycin (topical)

Mode of action -> bactericidal:

- bind irreversibly to the 16S ribosomal RNA and freeze the 30S initiation complex (30S-mRNA-tRNA) so that no further initiation can occur.
- also slow down protein synthesis that has already initiated and induce misreading of the mRNA.
- bind to the 16 S r-RNA and increase the affinity of the A site for t-RNA regardless of the anticodon specificity.
- May also destabilize bacterial membranes.

Aminoglycosides (bactericidal)

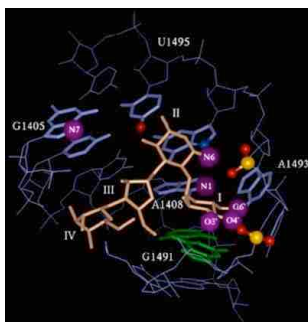


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Aminoglycoside Paromomycin bound to 16 S RNA



Aminoglycosides (bactericidal)

streptomycin, kanamycin, gentamicin, tobramycin, amikacin, netilmicin, neomycin (topical)

- **Spectrum of Activity** -Many gram-negative and some gram-positive bacteria; **Not useful for anaerobic** (oxygen required for uptake of antibiotic) or **intracellular bacteria**.
- **Resistance** - Common
- **Synergy** - The aminoglycosides synergize with β -lactam antibiotics. The β -lactams inhibit cell wall synthesis and thereby increase the permeability of the aminoglycosides.
- **BBB**: not penetrated
- Cave renal insufficiency

Aminoglycosides

- Not readily orally bioavailable, generally given im, iv

Resistance

- Inactivation by bacterial enzyme

Target infections:

- Gram- aerobs sepsis, Pseudomonas

Unwanted side effects

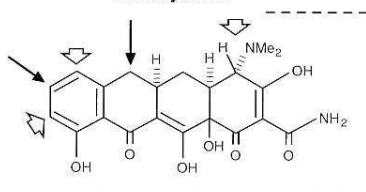
- Ototoxic
- Nephrotoxic
- Allergic reactions, anaphylaxis
- agranulocytosis

Tetracyclines (bacteriostatic)

tetracycline, minocycline and doxycycline

- **Mode of action** -> bacteriostatic: The tetracyclines reversibly bind to the 30S ribosome and inhibit binding of aminoacyl-t-RNA to the acceptor site on the 70S ribosome.
- **Spectrum of activity** - Broad spectrum; Useful against intracellular bacteria (ricketsia, mycoplasm, chlamydia, brucellosis, lyme disease, mixed respiratory tract infections), acne
- Reduced absorption in the presence of milk, antacids and calcium
- **Resistance** - Common, R plasmids
- **Adverse effects** - Destruction of normal intestinal flora resulting in increased secondary infections; staining and impairment of the structure of bone and teeth (not in pregnant and children).

Tetracycline



Critical Parts of the Molecule

- ↔ Sites of major modification
- Secondary modification sites
- - - Area critical for activity

Antimicrobials that Bind to the 50S Ribosomal Subunit

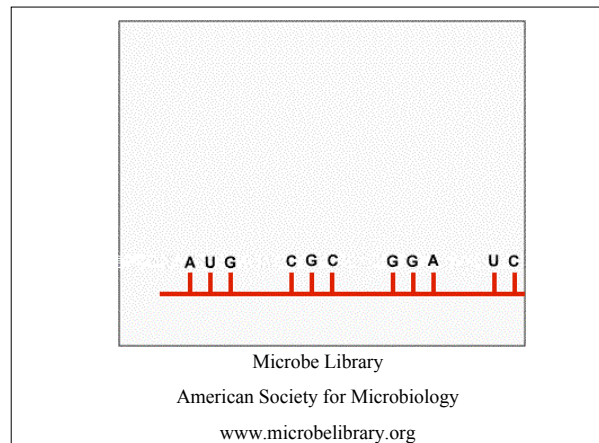
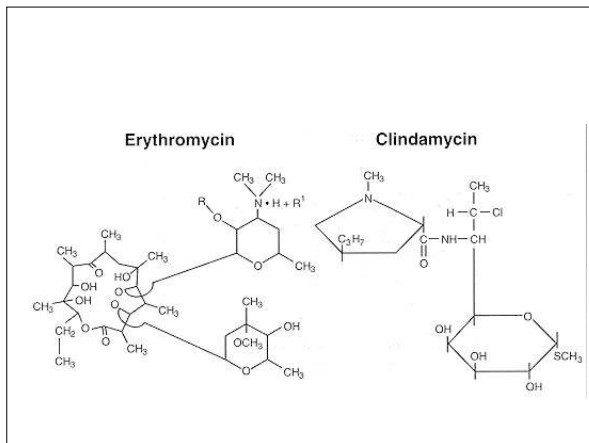
Chloramphenicol, Lincomycin, Clindamycin (bacteriostatic)

- **Mode of action** - These antimicrobials bind to the 50S ribosome and inhibit peptidyl transferase activity.
- **Spectrum of activity** - Chloramphenicol - Broad range;
Lincomycin and clindamycin - Restricted range
- **Resistance** - Common, CAT
- **Adverse effects** - Chloramphenicol is toxic (bone marrow suppression) but is used in the treatment of bacterial meningitis, if penicillins cannot be given (hypersensitivity).
- **Clindamycin** for gram+ cocci. Long half-life. cause pseudomembranous colitis with clostridium difficile!!

Macrolides (bacteriostatic)

erythromycin, clarithromycin, azithromycin, spiramycin

- **Mode of action** - The macrolides inhibit translocation.
- **Spectrum of activity** - Gram-positive bacteria, *Mycoplasma*, *Legionella*, *Chlamydia*
- **Resistance** - Common, R plasmid, alteration of binding site on bacterial ribosome
- **Elimination** by P450 cytochrome.
- **Unwanted side effects**: GIT, jaundice, hypersensitivity



Inhibitors of Nucleic Acid Synthesis

Inhibitors of RNA Synthesis

Selectivity due to differences between prokaryotic and eukaryotic RNA polymerase

Rifampin, Rifamycin, Rifampicin, Rifabutin (bactericidal)

- **Mode of action** - These antimicrobials bind to DNA-dependent RNA polymerase and inhibit initiation of mRNA synthesis.
- **Spectrum of activity** - Broad spectrum but is used most commonly in the treatment of tuberculosis
- **Resistance** - Common, chromosomal: modification of polymerase
- **Combination therapy** - Since resistance is common, rifampin is usually used in combination therapy.

Inhibitors of DNA Synthesis

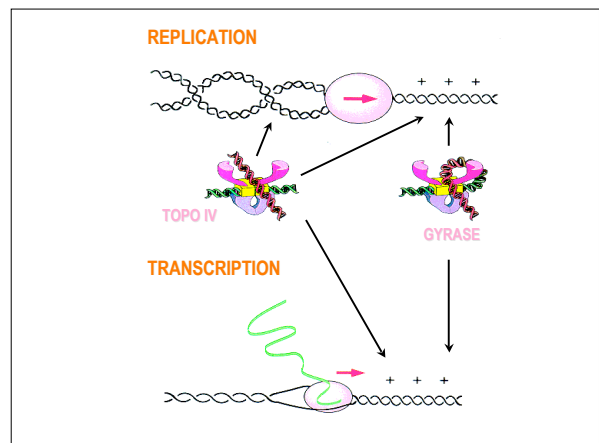
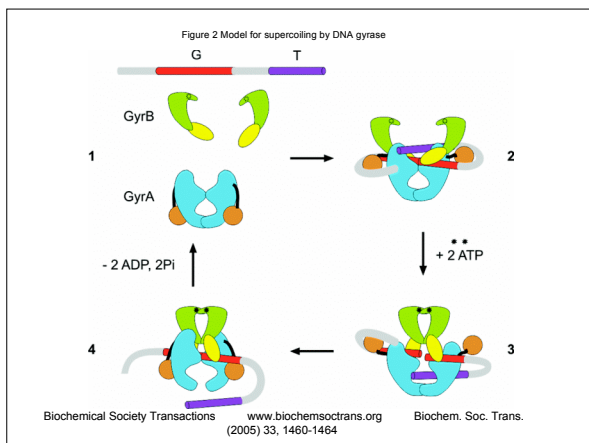
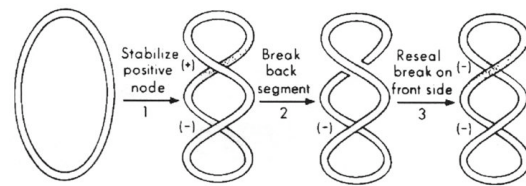
Selectivity due to differences between prokaryotic and eukaryotic enzymes

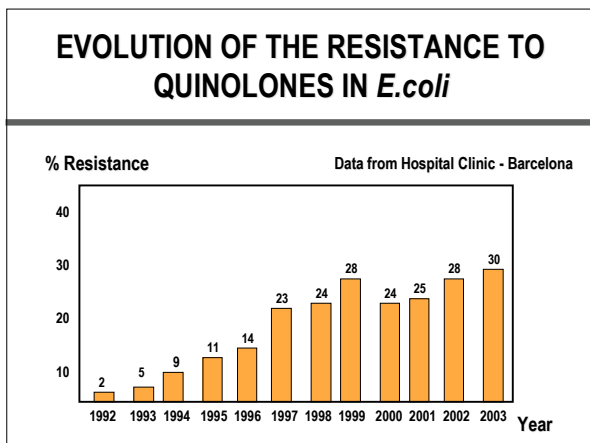
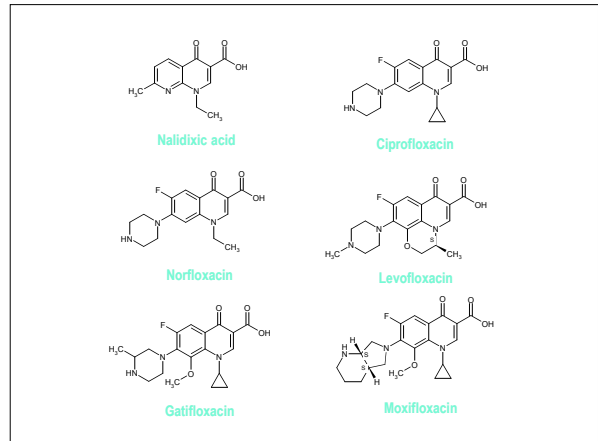
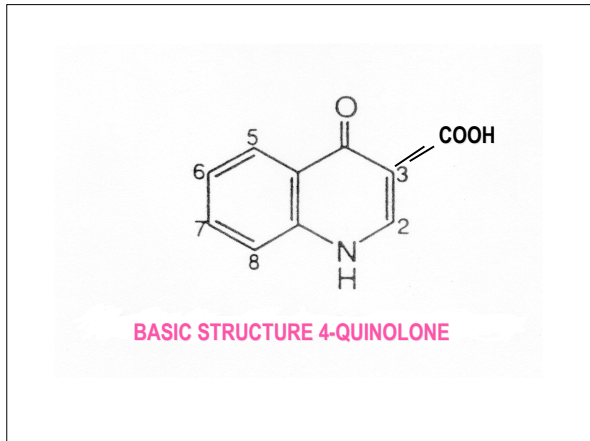
Quinolones (bactericidal)

nalidixic acid, ciprofloxacin, ofloxacin, norfloxacin, levofloxacin, lomefloxacin, sparfloxacin

- **Mode of action** - These antimicrobials bind to the A subunit of DNA gyrase (topoisomerase) and prevent supercoiling of DNA, thereby inhibiting DNA synthesis.
- **Spectrum of activity** - Gram-positive cocci and urinary tract infections. Enterobacteriaceae infections
- **Elimination** by P450 system
- Not + Theophyllin
- **Resistance** - Common for nalidixic acid; developing for ciprofloxacin
- **Unwanted side effects:** GIT, skin rash, arthropathy

Mechanism of Gyrase

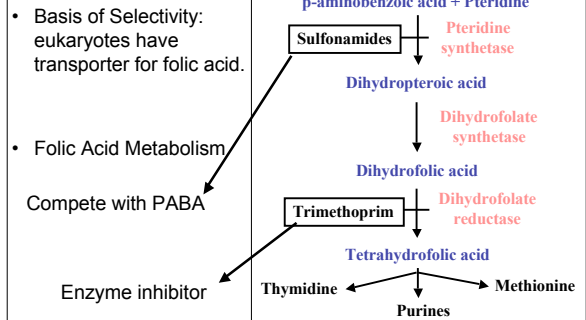




- ### MECHANISMS OF RESISTANCE TO QUINOLONES IN ENTEROBACTERIACEAE
- **Changes in the protein targets.**
 - DNA gyrase
 - Topoisomerase IV.
 - **Reduction in the accumulation of the quinolone.**
 - Decrease in permeability.
 - Increase in active efflux system(s).
 - **DNA gyrase and topoisomerase IV protection - R plasmid *qnr* gene->gene product binds to gyrase**

Antimetabolite Antimicrobials

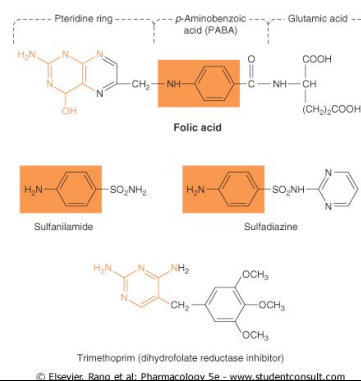
Inhibitors of Folic Acid Synthesis



Sulfonamides, Sulfones (bacteriostatic)

- **Mode of action** - These antimicrobials are analogues of para-aminobenzoic acid and competitively inhibit formation of dihydropteroic acid.
- Not active in the presence of pus and cell debris: rich in purines
- **Spectrum of activity** - Broad range activity against gram-positive and gram-negative bacteria; used primarily in urinary tract and *Nocardia* infections.
- **Resistance** - Common
- **Combination therapy** - The sulfonamides are used in combination with trimethoprim; this combination blocks two distinct steps in folic acid metabolism and prevents the emergence of resistant strains.

Structure of antifolate drugs



Trimethoprim, Methotrexate, Pyrimethamine (bacteriostatic)

- **Mode of action** - These antimicrobials binds to dihydrofolate reductase and inhibit formation of tetrahydrofolic acid.
- **Spectrum of activity** - Broad range activity against gram-positive and gram-negative bacteria; used primarily in urinary tract and *Nocardia* infections.
- **Resistance** - Common
- **Combination therapy** - These antimicrobials are used in combination with the sulfonamides; this combination blocks two distinct steps in folic acid metabolism and prevents the emergence of resistant strains.

Anti-Mycobacterial Antibiotics

Tuberculosis and leprosy

Isoniazid (INH) (bacteriostatic)

- **Mode of action** - Isoniazid inhibits synthesis of mycolic acids (fatty acid of mycobacterial cell wall). Only used for mycobacteria.
- **Spectrum of activity** - Used in treatment of tuberculosis
- Elimination: slow vs rapid acetylators
- **Resistance** - Has developed due to reduced penetration
- Allergic reactions

Further 'anti-TB' drugs

Rifampicin

- **Blocks RNA polymerase**
- **Rapid resistance due to modification of polymerase**

Ethambutol

Pyrazinamide

**AIDS + insufficient treatment ->
Multi-drug resistance great problem
(MDR M. tuberculosis)**

Therapy of tuberculosis

- First-line drugs
 - Isoniazid
 - Rifampin
 - Pirazinamide
 - Ethambutol
- All taken for 2 months
- Isoniazid and Ethambutol taken for 6 months
- Direct supervision of health care professionals
- Non-compliance due to lengthy drug treatment

→ DRUG RESISTANCE

MDR-TB

- Multi-drug resistant tuberculosis
- Strains of Mtb resistant to both isoniazid and rifampin
 - Two most important drugs
- Resistance to both results in an inability to control TB with other first-line drugs
- Need to use second-line drugs
 - More toxic, less effective
 - Treatment prolonged, expensive
 - Difficult in resource-limited settings

MDR-TB

Table IV. Suggested treatment for patients with MDR-TB

Resistance pattern	Initial phase		Continuation phase	
	Drugs	Minimum duration (months)	Drugs	Minimum duration (months)
Resistance to isoniazid and rifampicin with or without resistance to streptomycin	Aminoglycoside	3	Ofloxacin or levofloxacin	18-24
	Ofloxacin or levofloxacin		Ethambutol	
	Pyrazinamide		Ethionamide	
	Ethambutol			
Resistance to isoniazid, rifampicin and ethambutol with or without resistance to streptomycin	Aminoglycoside	3	Ofloxacin or levofloxacin	18-24
	Ofloxacin or levofloxacin		Ethionamide	
	Pyrazinamide		Cycloserine	
	Ethionamide			

During the continuation phase antituberculosis drugs are administered for a period of at least 18 months after sputum conversion
Source: Refs. 15,119

Sharma and Mohan 2004

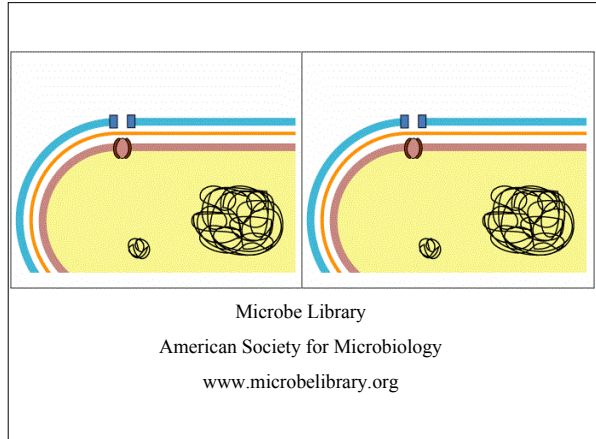
XDR-TB

- Increased use of second-line drugs for treatment of MDR-TB has led to resistance
- Emergence of XDR-TB (extensively or extremely drug resistant tuberculosis)
- 2000-2004: international survey of TB care facilities
 - 20% of TB cases MDR, 2% XDR
- Essentially untreatable, high risk of mortality
 - South Africa study:
 - 53 cases XDR-TB (10% of reported TB cases)
 - 52/53 have since died

→ NEED NEW DRUGS

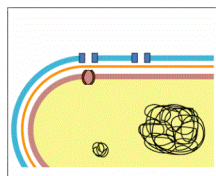
Antimicrobial Drug Resistance Mechanisms

- Altered permeability
 - Altered influx
 - Gram negative bacteria



Antimicrobial Drug Resistance Mechanisms

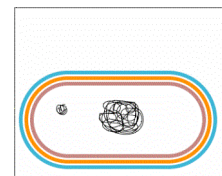
- Altered permeability
 - Altered efflux
 - tetracycline



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Antimicrobial Drug Resistance Mechanisms

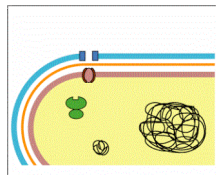
- Inactivation
 - β -lactamase
 - Chloramphenicol acetyl transferase



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Antimicrobial Drug Resistance Mechanisms

- Altered target site
 - Penicillin binding proteins (penicillins)
 - RNA polymerase (rifampin)
 - 30S ribosome (streptomycin)



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Antimicrobial Drug Resistance Mechanisms

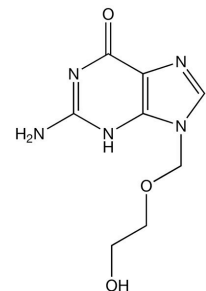
- Replacement of a sensitive pathway
 - Acquisition of a resistant enzyme (sulfonamides, trimethoprim)

Viral infections with available antiviral drugs

- **Herpes viruses (HSV, VSV und CMV)**
- **HIV**
- **Hepatitis B virus (HBV)**
- **Hepatitis C virus (HCV)**
- **Influenza A und B (Flu A/B)**
- **Respiratory syncytial virus (RSV)**

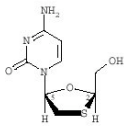
Antivirals for Herpesviruses

- Acyclovir/Zovirax
- Guanin analogue
- Phosphorylated preferentially by viral thymidin kinase
- Disrupts viral DNA replication
- Used to treat
 - genital herpes, simplex II
 - Shingles (chickenpox virus)
 - Cytomegal Virus (CMV) in those immunocompromized with AIDS
- Limited adverse reactions



Nukleosidanalogues for HBV

Lamivudine, 3TC
oral, 100 mg/Tag



Additional:
Famciclovir
Adefovir
Entecavir

After 12 months:
1. Suppression of viral load
2. Normalized liver enzymes
3. Normalized liver histology

In 60 % of Patients

Mutations in der HBV Polymerase cause resistance to nucleoside analogues

HBV: YMDD-mutations found in 16-40% of the lamivudin-treated patients after 12 months

HBV therapy is there, where HIV treatment was 1993

Zhou et al, 2001

HBV and HCV: Interferon- α

- Pleiotropic functions
 - Antiviral activity
 - Regulation of cell proliferation
 - Induction of MHC expression

IFN-Therapy für chronic hepatitis B

- 5-10 million units per injection (s.c) 3x per week for 24 weeks
- 15%-40% patients show lasting efficacy
- Severe unwanted side effects:
 - Flu-like symptoms, fatigue, nausea
- Mechanism of action specifically for HBV not clear

Hepatitis C Virus

- RNA virus, *Flaviviridae*
- +ss RNA genome 9.6 kb
- 50-80% chronic
- No vaccine!
- Chronic carriers appr. 1 % ww
- Major cause of liver cirrhosis and HCC

Interferon-Therapie der chronischen Hepatitis C

- **Recombinant Interferons**
 - Human interferon 2a/2b
 - Consensus-interferon
 - Pegylated Interferon
- **In combination with Ribavirin**
- **Indications**
 - HCV RNA positive for at least 6 months
 - increased liver enzymes
- **Successful therapy more likely if**
 - low HCV RNA Titer
 - non-genotype 1
 - young age
 - no cirrhosis

Successrate in the treatment of chronic HCV

- **INF monotherapy**
 - 50% improved liver enzymes
 - 25% eliminate virus
- **Combination with ribavirin: Permanent response in 40 %**
- **Remaining patients at least show improved liver histology and reduced risk of HCC**

IFN-Ribavirin-Therapy for chronic Hepatitis C

		Virus titer	
		>2 Meq*/ml	<2MEq/ml
IFN- α : 3X 3 Million IE/week Or <u>Peginterferon</u> Ribavirin: 1-1,2 g/day	Genotype 1	12 months	6 months
	Genotype 2 und 3	6 months	6 months

*million HCV genome equivalents

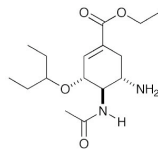
Treatment of influenza: Neuramidase inhibitors

Zanamvir (Relenza)

- inhalation powder
- Flu A + B
- Start within 48 h of onset of disease
- USE: bronchospasm

Oseltamivir (Tamiflu)

- Oral prodrug
- Flu A + B
- competitive inhibition of the enzyme
- Start within 48 h of onset of disease
- Reduces time to improvement by 1.3 d



Resistance still rare (Study from Japan with highest use)

Viral neuraminidase...

catalyzes the cleavage of the linkage between a terminal sialic acid and adjacent sugar residue and thereby

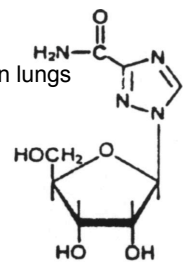
- promotes the release of virions from infected cells
- promotes the penetration of virus into respiratory epithelial cells
- prevents the formation of viral aggregates
- prevents viral inactivation by respiratory mucus
- induces cellular apoptosis by activating transforming growth factor beta
- and induces cytokines including interleukin-1 and tumor necrosis factor.

Amantadine/Rimantadine

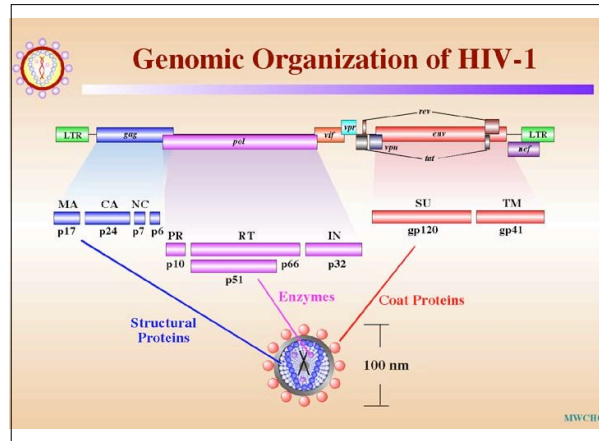
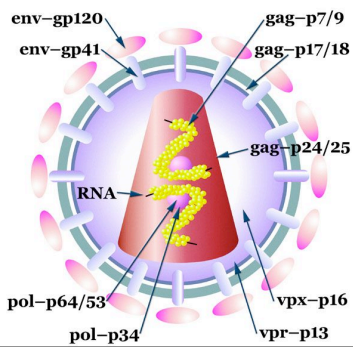
- Interfere with M2 (ion channel) and thus blocks uncoating in endosome
- Flu A only
- Give within 2 days of onset
- High level of resistance, not really a drug of choice anymore
- Cross-resistance
- Single aa mutations causes resistance

Ribavirin

- Nucleoside analogue
- Inhaled gives high concentrations in lungs
- Good for children with RSV
- Lassa, flaviviruses
- Activated by cellular kinases
- Mode of action
 - Hypermutation due to mispairing
 - Inhibit viral RNA dependent polymerases
 - Blocks cap snatching (viral guanylyl transferase)
 - Promotes switch from type 2 to type 1 T cell response



Targeting HIV-1: the largest antiviral arsenal available



HIV virus and T cell dynamics

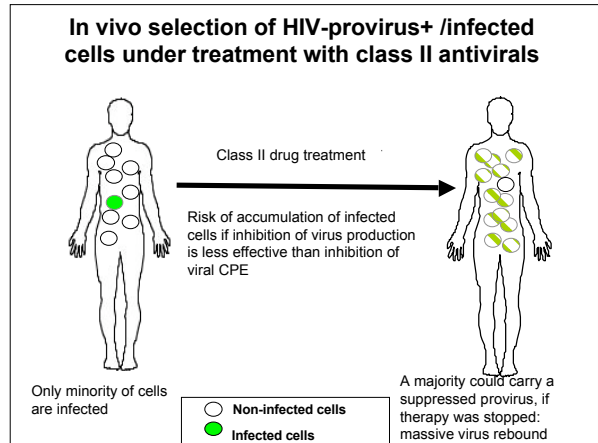
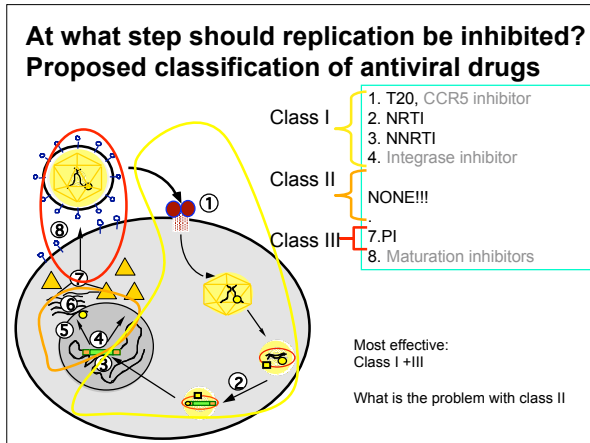
- Half-life of
 - Virion: 6 h
 - Infected CD4+ cells: 0.7 days
- Average virus production:
 - 10^{10} Virions per day
 - Each mutation occurs many times per day

Perelson et al., 1996

Aim of Therapy:
Suppress virus replication permanently and completely to limit resistance

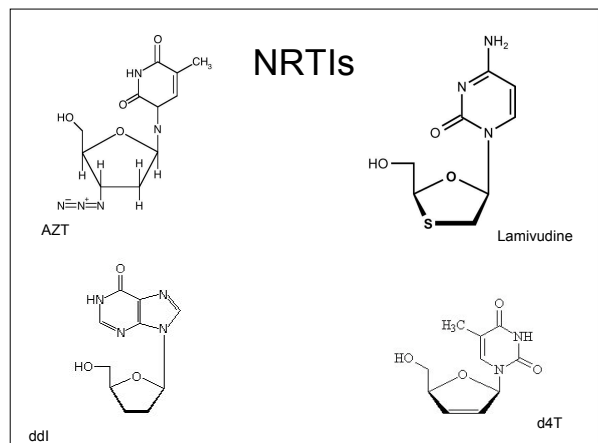
Antivirals to treat advanced HIV

- 25 approved compounds or combinations, see table
- NRTI
- NNRTIS
- PI
- Fusion inhibitors
- Novel targets in clinical development: IN, CCR5



Nucleoside reverse transcriptase inhibitor: Nukes or NRTIs

- Compete with natural nucleosides for HIV RT
- Modifications on ribose
- Incorporation into nascent chain leads to chain termination
- Require phosphorylation by cellular kinase
- Cellular nuclear DNA pol is resistant, but mitochondrial DNA pol is sensitive



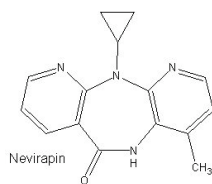
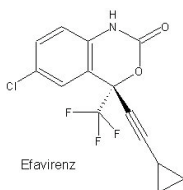
NRTI

- AZT+D4T Thymidin analogues
- FTC + 3TC cytidine analogues
 - Don't combine analogues to same nucleoside
- Strong cross-resistance
- Renal excretion
- Toxicity: Myelotoxic, polyneuropathy, pancreatitis, mitochondrial toxicity, hypersensitivity (ABC)
- Lamivudine has few side effects but rapid cross-resistance induction, also given for HBV

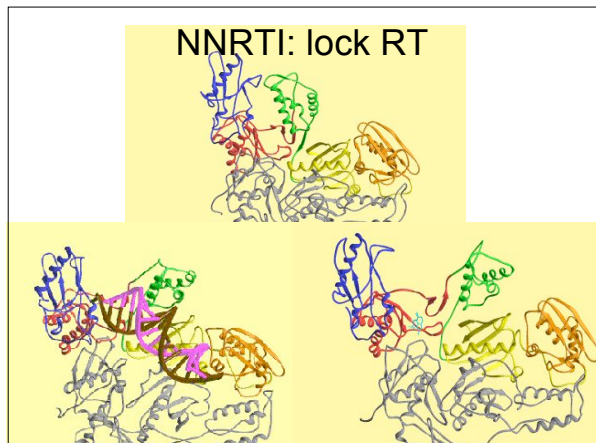
Non-nucleoside reverse transcriptase inhibitors (NNRTI)

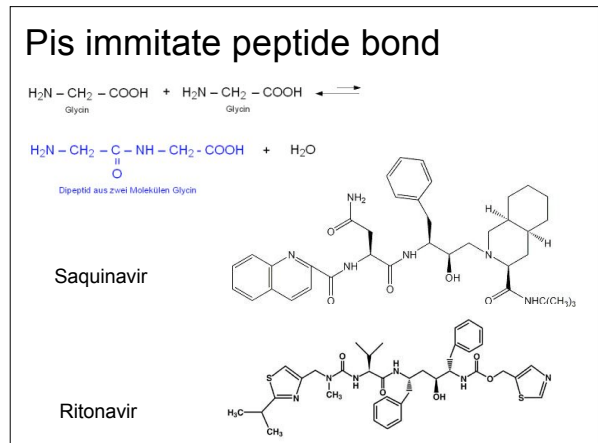
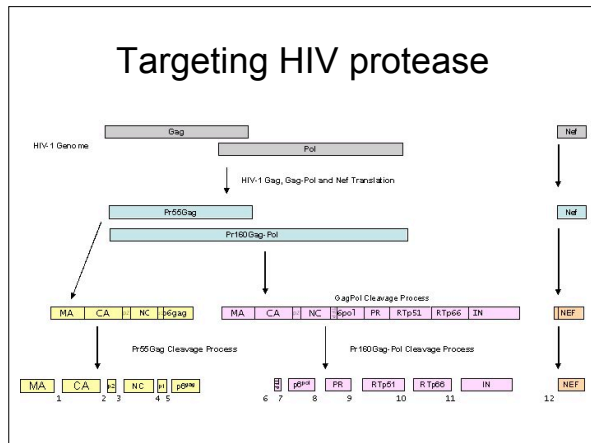
- Bind and inactivate RT
- EFZ, NVP
- Not effective as monotherapy
- Always in combination, e.g. AZT+ddI+NVP =classic
- Resistance rapid and mostly cross-resistance: K103N in RT causes resistance to all 3 NNRTI members.
- Resistant viruses not attenuated!
- If resistance is found, therapy is useless.
- Few unwanted side effects
- Metabolized by Cytochrom P450

NNRTI



NNRTI: lock RT





Protease Inhibitor

- Inhibit viral protease by binding and blocking active center of enzyme

- ### Pis
- All have comparative efficacy
 - Ritonavir not alone
 - Cross resistance
 - High pill burden
 - GI-side effects, Lipodystrophy, Dyslipidaemia
 - CYP3A4 System, ritonavir inhibition of system->boost effect
 - ✓ reduces resistance
 - ✓ Name + 'r' indicates addition of ritonavir: saquinavir/r

Mortality rate after PI introduction in patients with < 100 CD4 lymphocytes

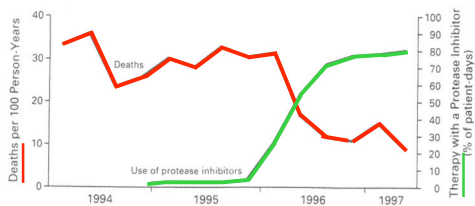
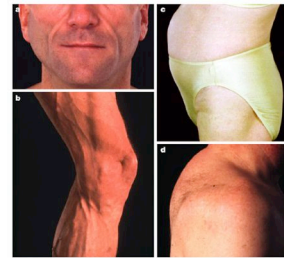


Figure 1 Mortality rate in a cohort of 1255 HIV- seropositive patients with less than 100 CD4+ cells/mm³ and the frequency of use of protease inhibitors. (From Ref. 3.)

Lipodystrophy



Nature Reviews | Drug Discovery

Lipodystrophy syndrome

- abnormal deposition and distribution of fat in the body
- peripheral and hepatic insulin resistance
- impaired glucose tolerance
- type 2 diabetes
- hypertriglyceridemia
- hypercholesterolemia
- increased free fatty acids (FFA)
- decreased high density lipoprotein (HDL)

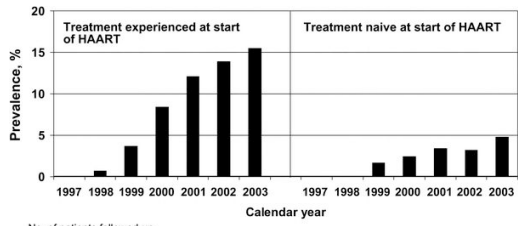
Error rates of viral RTs and DNA polymerase

Assay	Enzyme	Error rate	Reference
ϕX 174 DNA reversion assay	HIV-1 RT	1/4000	Preston et al., 1988
	AMV RT	1/9000	Preston, et al., 1988
	DNA polymerase-β	1/8000	Kunkel and Loeb, 1981
	DNA polymerase-α	1/30 000	Loeb and Perrino, 1990
M13mp2 DNA forward mutation assay	DNA polymerase-α primase	1/460 000	Reyland and Loeb 1987
	HIV-1 RT	1/4800	Bebenek et al., 1989
	AMV RT	1/17 000	Roberts et al., 1988
	M-MuLV RT	1/30 000	Roberts et al., 1988
	Taq DNA polymerase	1/9000	Tindall and Kunkel 1988
SV40 DNA polymerase complex	DNA polymerase-β	1/14 000	Roberts and Kunkel 1988
	DNA polymerase-α primase	1/150 000	Roberts and Kunkel 1988

Quasispecies: complex genetically related virus species

HAART failure

CSH



No. of patients followed-up													
554	1482	1814	1944	1988	2029	2028	140	514	716	860	958	1174	
0	10	68	163	241	282	315	0	0	10	21	33	38	
No. of patients with triple drug-class treatment failure													