Recent advances of drug therapy of Acquired Immune Deficiency Syndrome (HIV treatment)

Pharmacology Literature Review

Group 20 – 2003/04 Batch

Jayasundera J. M.	M/03/180
Jayatilaka G. S.	M/03/74
Jayawardana J. M. P. R.	M/03/75
Jayaweera P.M.E.D (Miss)	M/03/76
Jothipala S. D.	M/03/77
Kahingala B. D.	M/03/78

Introduction

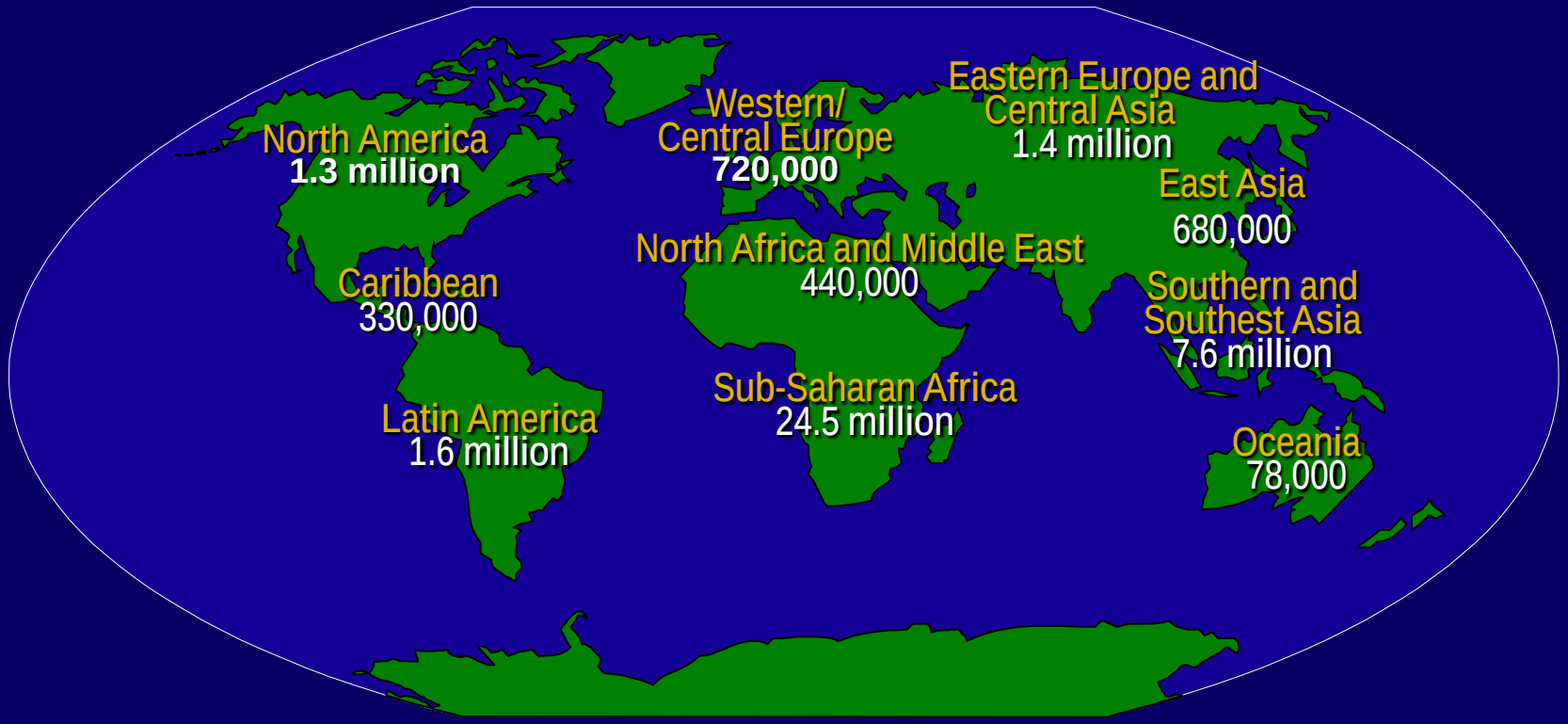
- Acquired Immune Deficiency Syndrome (AIDS) is the most serious stage of Human Immunodeficiency Virus (HIV) infection.[1]
- Results from the destruction of the infected person's immune system
- HIV types (HIV-1, HIV-2) are derived from retrovirus
- The illness was first described in 1981[1]

- If a person is infected with HIV and his CD4+ T cell count drops below 200 (cells/mm3) or develops an AIDS-defining condition, that person has AIDS.[2]
- AIDS-defining conditions are various opportunistic infections of fungal, bacterial, viral and protozoan origin as well other diseases like neoplasm, wasting syndrome etc.[2]

1 Brooks GF, Butel JS, Morse SA: AIDS & Lentivirus: Jawetz, Melnick, & Adelberg's Medical microbiology 23rd ed. McGraw-Hill 2004; pg 605-62

2 Guidelines for National Human Immunodeficiency Virus Case Surveillance: MMWR 1999; 48(RR13):1-31. http:// www.cdc.gov

Epidemiology



A global view of HIV infection : 38.6 million people [33.4-46.0 million] living with HIV, 2005

HIV was declared as a global emergency in 2003

Estimated number of people living with HIV in Sri Lanka	
Adults and children 2005	Adults and children 2003
5000 [3000 – 8300]	3100 [1900 – 4400]

UNAIDS (2006). Country profile: 2006 Report on the global AIDS epidemic. UNAIDS, Geneva. August,2006. http://www.unaids.org

HIV treatment

Objectives

- Reduce HIV related morbidity & mortality
- Improve quality of life
- Restore & preserve immunologic function
- Suppress viral load Maximally & durably

HIV treatment

- → **Counselling**
- → **Drug therapy** → **Highly Active Antiretroviral Therapy (HAART)**
  (Combination antiretroviral therapy)

Indications – Drug Therapy

- All patients with AIDS-defining illness
- Asymptomatic patients with <200 CD4+ T cells/mm3

Bartlett JB et al: Guidelines for the Use Reviewed of Antiretroviral Agents in HIV-Infected Adults and Adolescents.DHHS-USA 2006;1:40.

Classes of antiretroviral drugs

1. Nucleoside Reverse Transcriptase Inhibitors (NRTI)
2. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)
3. Protease Inhibitors (PI)

NRTIs

Abacavir (ABC)
Didanosine (ddI)
Emtricitabine (FTC)
Lamivudine (3TC)
Stavudine (d4T)
Tenofovir (TDF)
Zalcitabine (ddC) *withdrawn 2005*
Zidovudine (ZDV)
3TC/ABC
3TC/ABC/ZDV
3TC/ZDV
FTC/TDF

NNRTIs

Delavirdine (DLV)
Efavirenz (EFV)
Nevirapine (NVP)

PIs

Amprenavir (APV) *discontinued 2004*
Atazanavir (ATV)
Darunavir (DRV)
Fosamprenavir (FPV)
Indinavir (IDV)
Lopinavir/ritonavir (LPV/RTV)
Nelfinavir (NFV)
Ritonavir (RTV)
Saquinavir (SQV hgc)
Tipranavir (TPV)

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Guidelines for AIDS Therapy - 2006

Recommended Components of Antiretroviral Therapy		
NRTIs	**NNRTIs**	**PIs**
Tenofovir (TDF) / Emtricitabine (FTC)†	Efavirenz (EFV)	Lopinavir (LPV) / Ritonavir (RTV)
Zidovudine (ZDV) / Lamivudine (3TC)‡	Nevirapine (NVP)	Atazanavir (ATV) / Ritonavir (RTV)
Abacavir (ABC) / Lamivudine (3TC)‡		Fosamprenavir (FPV) / Ritonavir (RTV)

†Or 3TC. ‡Or FTC.

2nd line therapy should consist of 2 NRTIs + 1 PI or 2 NRTIs + 1 NNRTI

TDF 300 mg/day +
FTC 200 mg/day +

LPV/RTV 400/100 mg twice daily
+ 2 **NRTI**s

ZDV/3TC 300/150 mg twice daily +
EFV 600 mg/day

WHO. Recommendations for treatment, care and support for people living with HIV infection and AIDS in resource limited settings. WHO 2006;21-22

Choice of second line ARVs for treatment failure, Antiretroviral therapy for HIV infection in adults and adolescents in resource limited settings. WHO 2006;46-48

Novel Antiretrovirals in Clinical Development

Entry inhibitors

- Maraviroc
- Vicriviroc
- AMD 070
- TNX-355
- PRO140
- CCR5mAb004

Integrase inhibitors

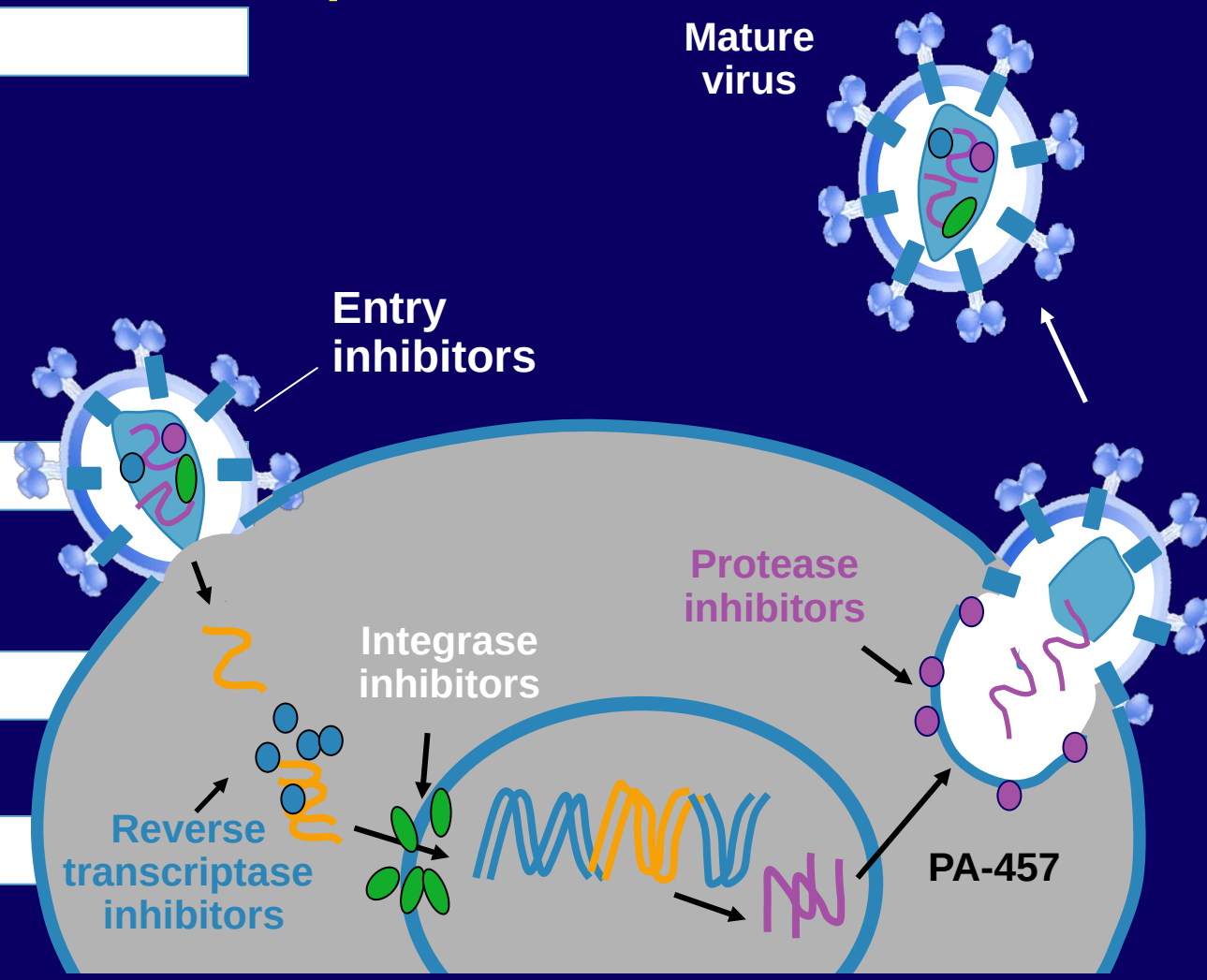
- GS-9137
- MK-0518

Maturation inhibitors

- PA-457

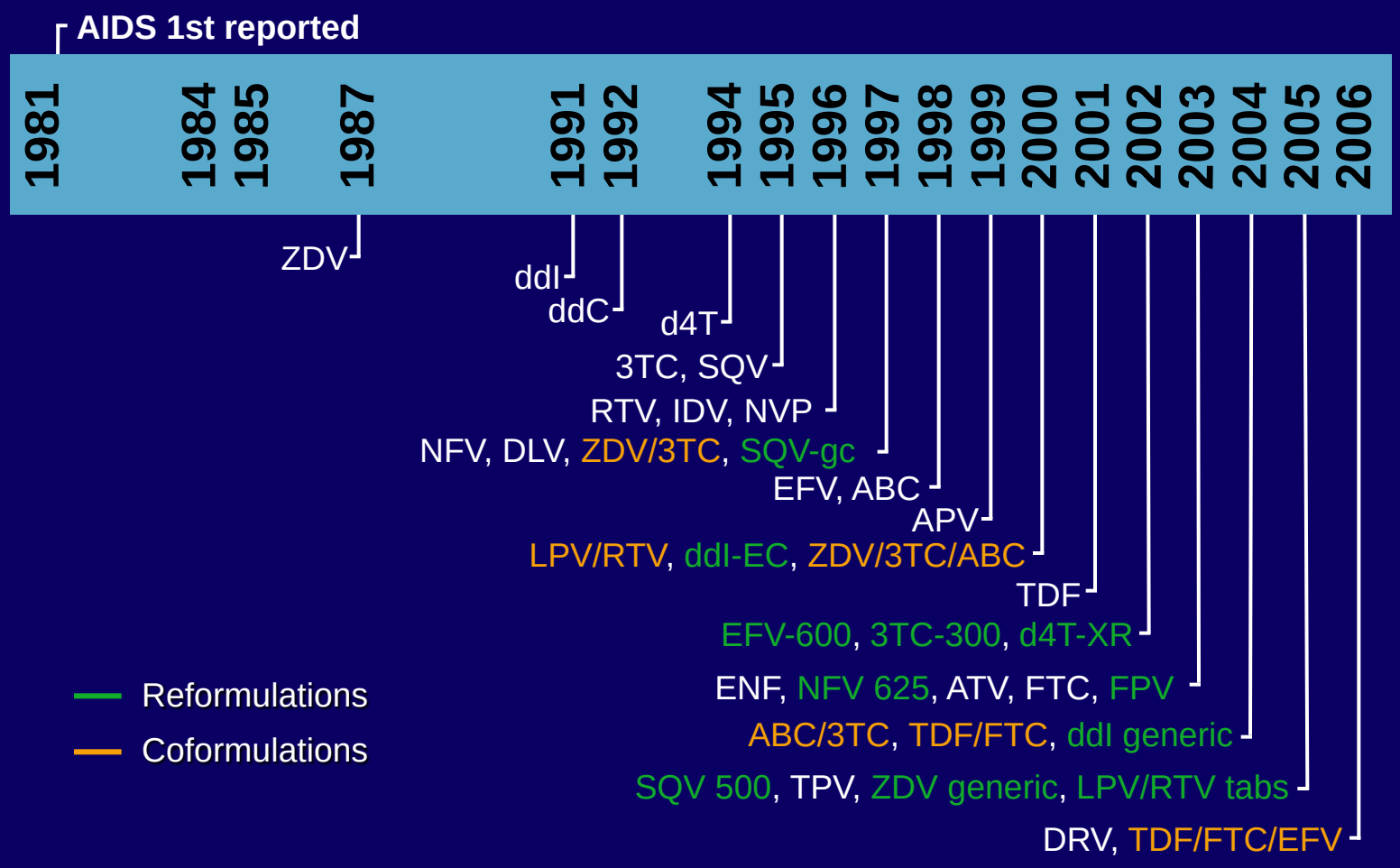
Fusion inhibitor

- Enfuvirtide



Eron JJ. Clinical Data and Development of Agents in Novel Antiretroviral Classes. Program and abstracts of the XVI International AIDS Conference; August 13-18, 2006; Toronto, Canada. http:// www.clinicaloptions.com/novelclasses

Timeline of Antiretroviral Development



Pozniak AL, Squires KE.. Advances in Antiretroviral Options. Program and abstracts of the XVI International AIDS Conference; August 13-18, 2006; Toronto, Canada. http:// www.clinicaloptions.com/novelclasses

Dosing Evolution of HIV Drugs

Agent	Original Daily Dosing	Current Daily Dosing
ZDV	12	2
ddI	4	1
d4T	2	1
3TC	2	1
EFV	3	1
NFV	9	4
SQV	9	6 (SQV/RTV)
APV	16	4 (FPV/RTV)
LPV/RTV	6	4

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- Advantages of Fixed-Dose Formulations
  - Reduced pill burden
  - Increased adherence
  - Improved patient satisfaction
  - Reduced risk of dosing errors
  - Allowance for once-daily administration

Non-recommended therapy

- Monotherapy with NRTI or NNRTI
- Dual-NRTI regimens alone
- Triple-NRTI regimens

Pozniak AL, Squires KE.. Advances in Antiretroviral Options. Program and abstracts of the XVI International AIDS Conference; August 13-18, 2006; Toronto, Canada. http:// www.clinicaloptions.com/novelclasses

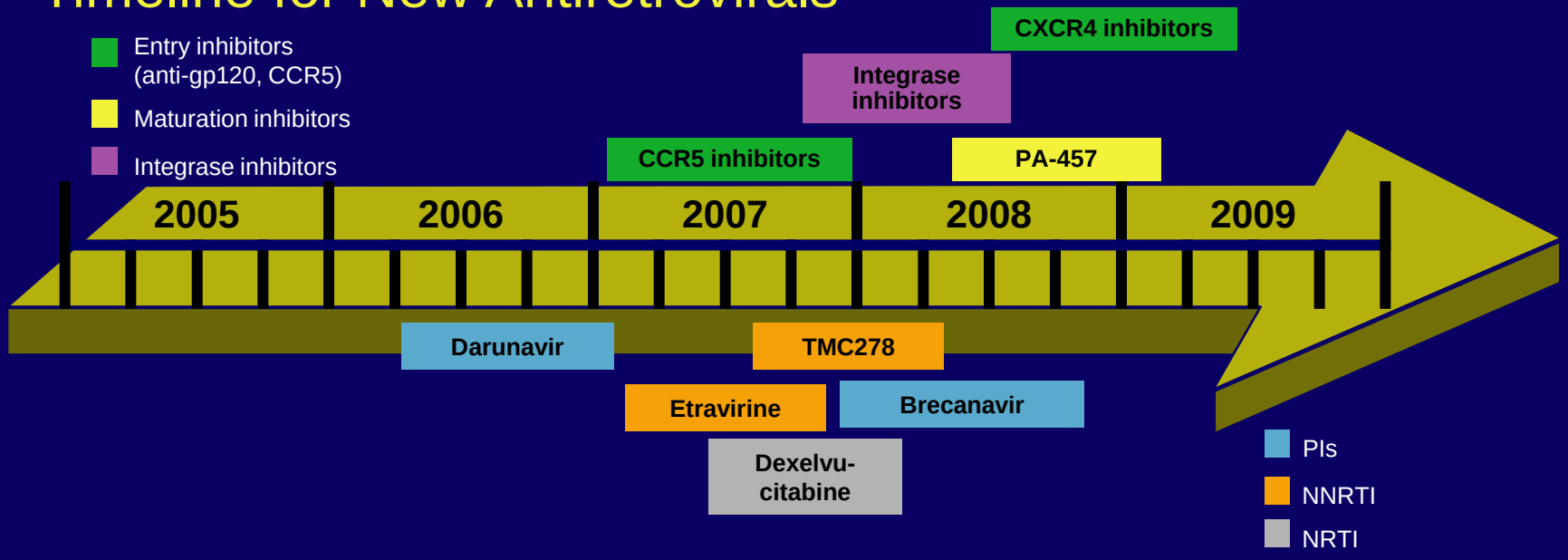
Future

Vaccine

The scientific consensus is that an HIV/AIDS vaccine is a achievable goal.

Vaccine approaches – Recombinant subunit, Recombinant vector, DNA, Combination, Live-attenuated, Whole-inactivated[1]

Timeline for New Antiretrovirals[2]



1 Milley L. The science of HIV/AIDS vaccines.ICASO:2003;13:15. www.icaso.org
2 Eron JJ. Clinical Data and Development of Agents in Novel Antiretroviral Classes. Program and abstracts of the XVI International AIDS Conference; August 13-18, 2006; Toronto, Canada. http:// www.clinicaloptions.com/novelclasses

Conclusion

- Reformulation of existing agents
- Development of coformulations of 2 or more agents
- Approval of new agents
- Identification of novel agents and new approaches to therapy

Thank You

References

Brooks GF, Butel JS, Morse SA: AIDS & Lentivirus: Jawetz, Melnick, & Adelberg's Medical microbiology 23rd ed. McGraw-Hill 2004; pg 605-62

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