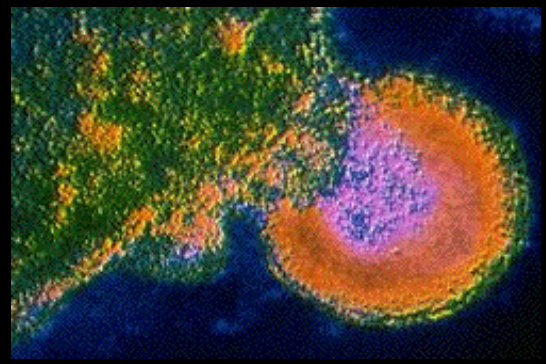
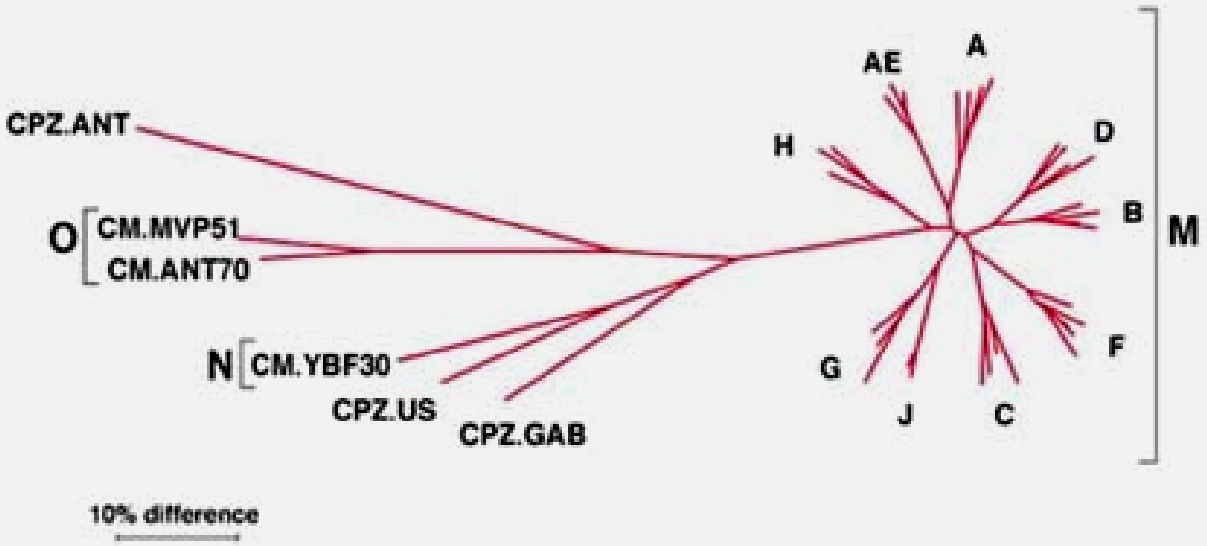


HIV-1 Subtypes: An Overview

Anna Maria Geretti

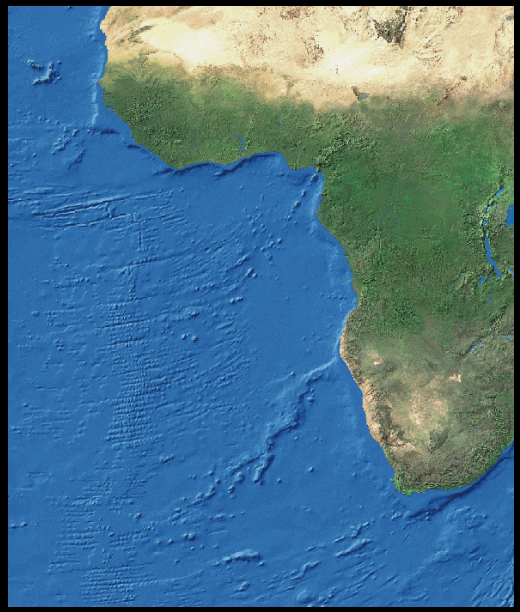
Royal Free Hospital

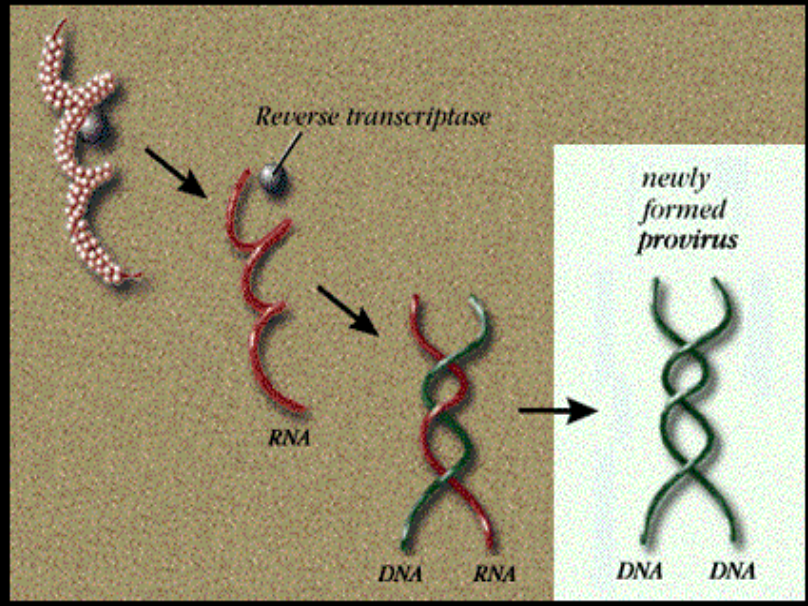
Genetic Subtypes of HIV-1



Group M Subtypes

- A (1, 2, 3)
- B
- C
- D
- F (1, 2)
- G
- H
- J
- K

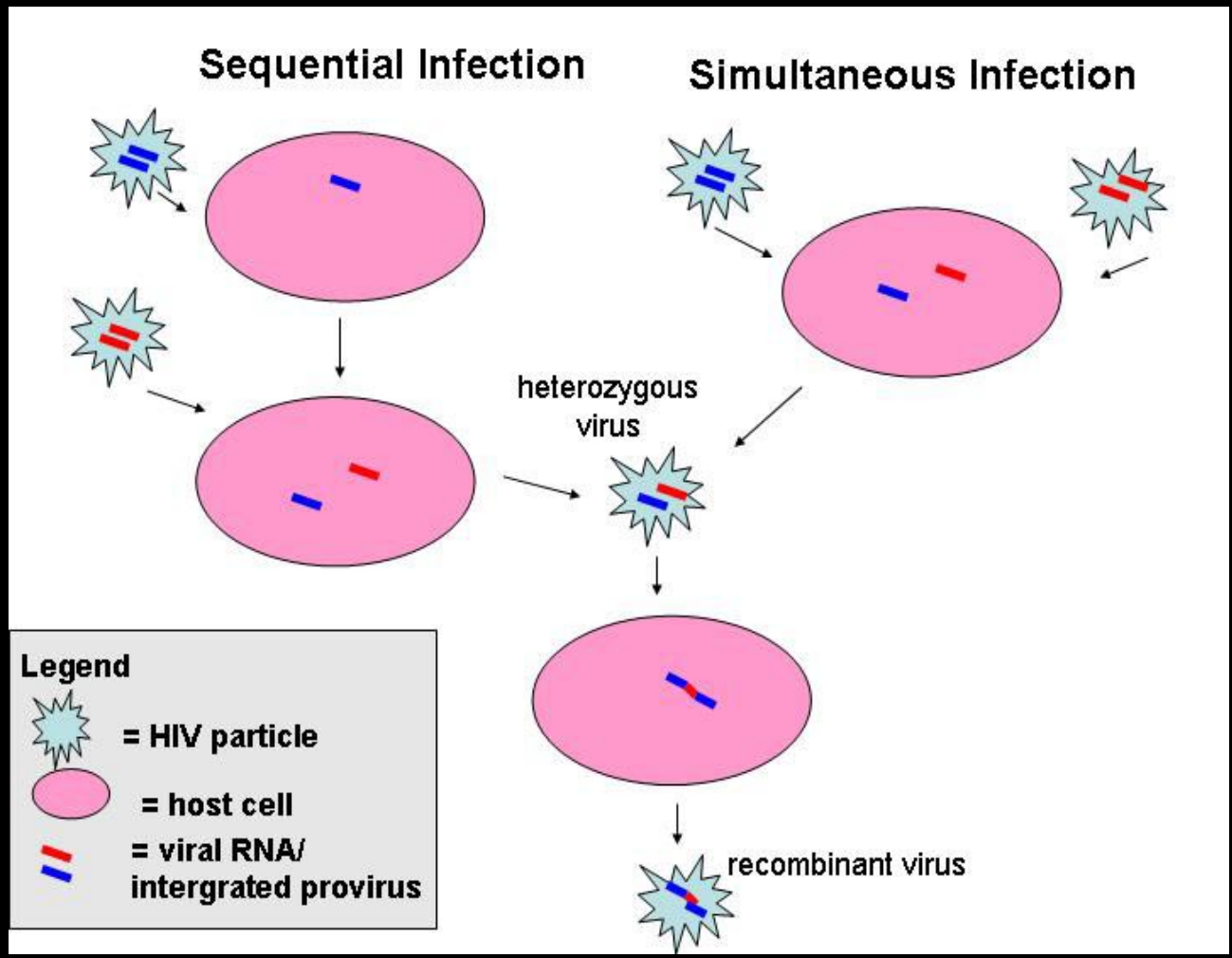




Mechanisms of HIV-1 genetic diversification

- **Point mutations**
  - RT error rate: ~1 per genome round
- **Recombination between strains**
  - Recombination rate: 7-30 per genome round

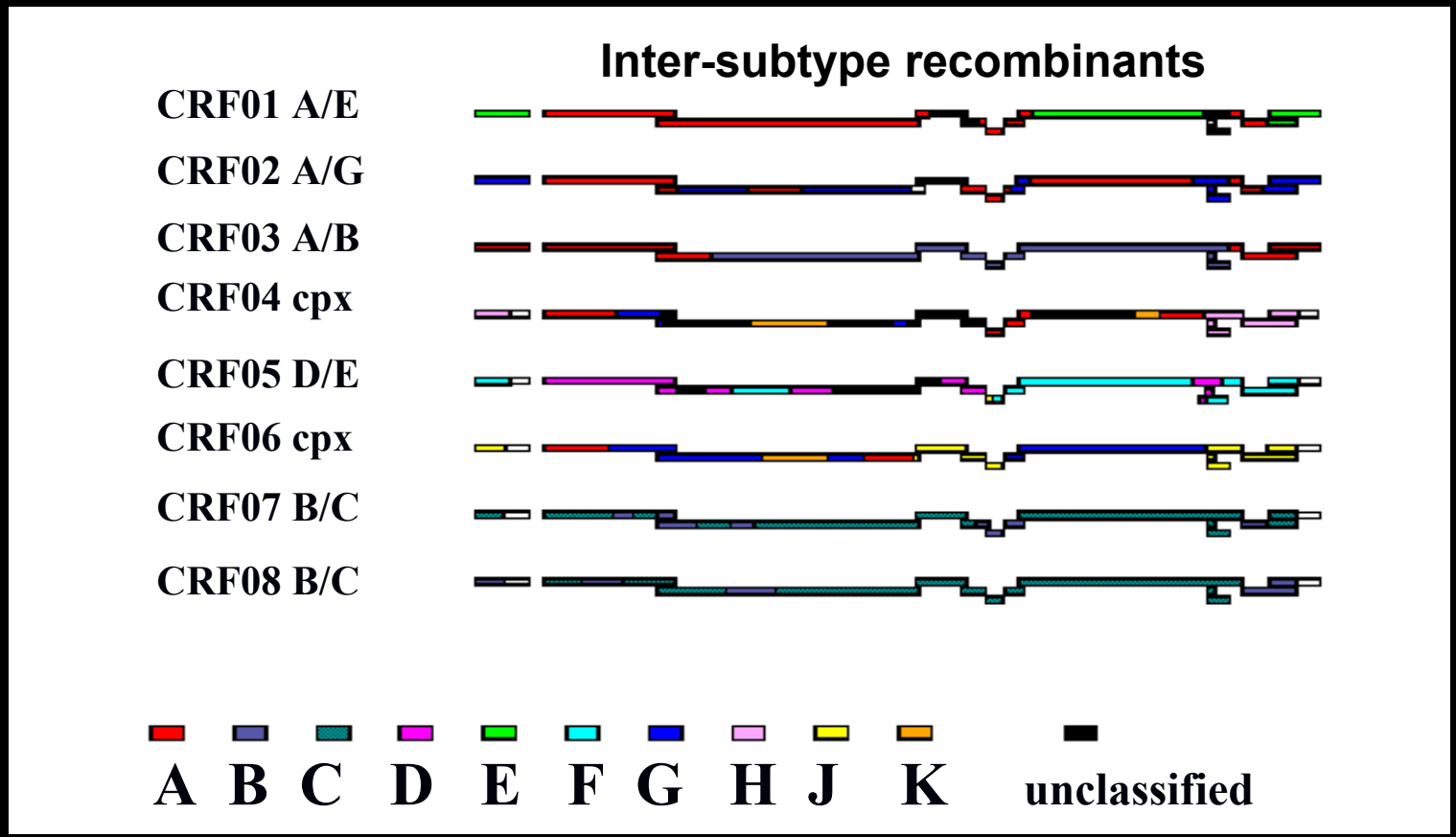
Recombination



- Inter-group
- Inter-subtype
- Intra-subtype
- Intra-species

Circulating Recombinant Forms (CRFs)

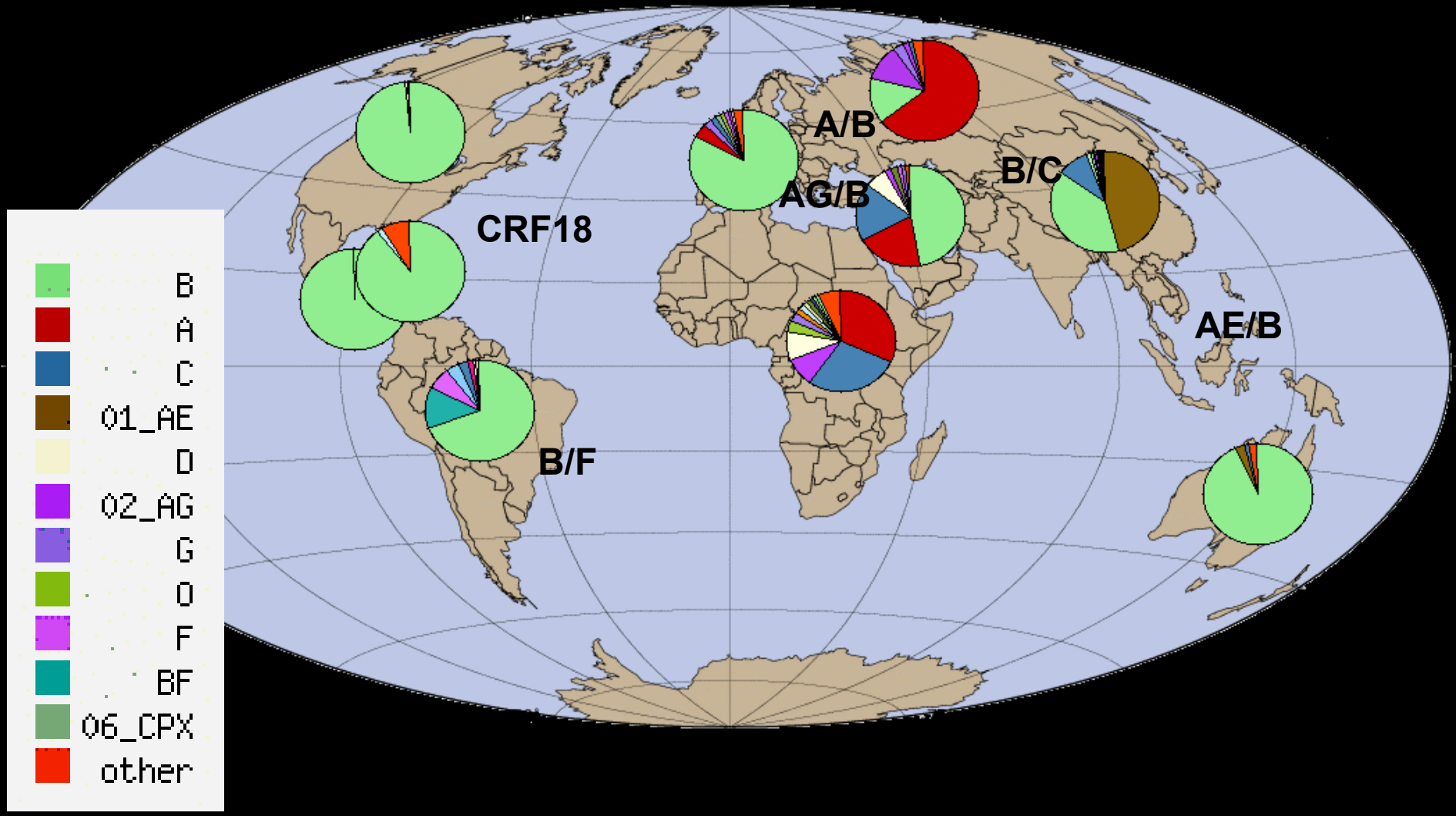
- Recombinant HIV-1 genomes that have infected ≥3 persons who are not epidemiologically related
- Can be assumed to make an epidemiologically relevant contribution to the HIV-1 M group epidemic



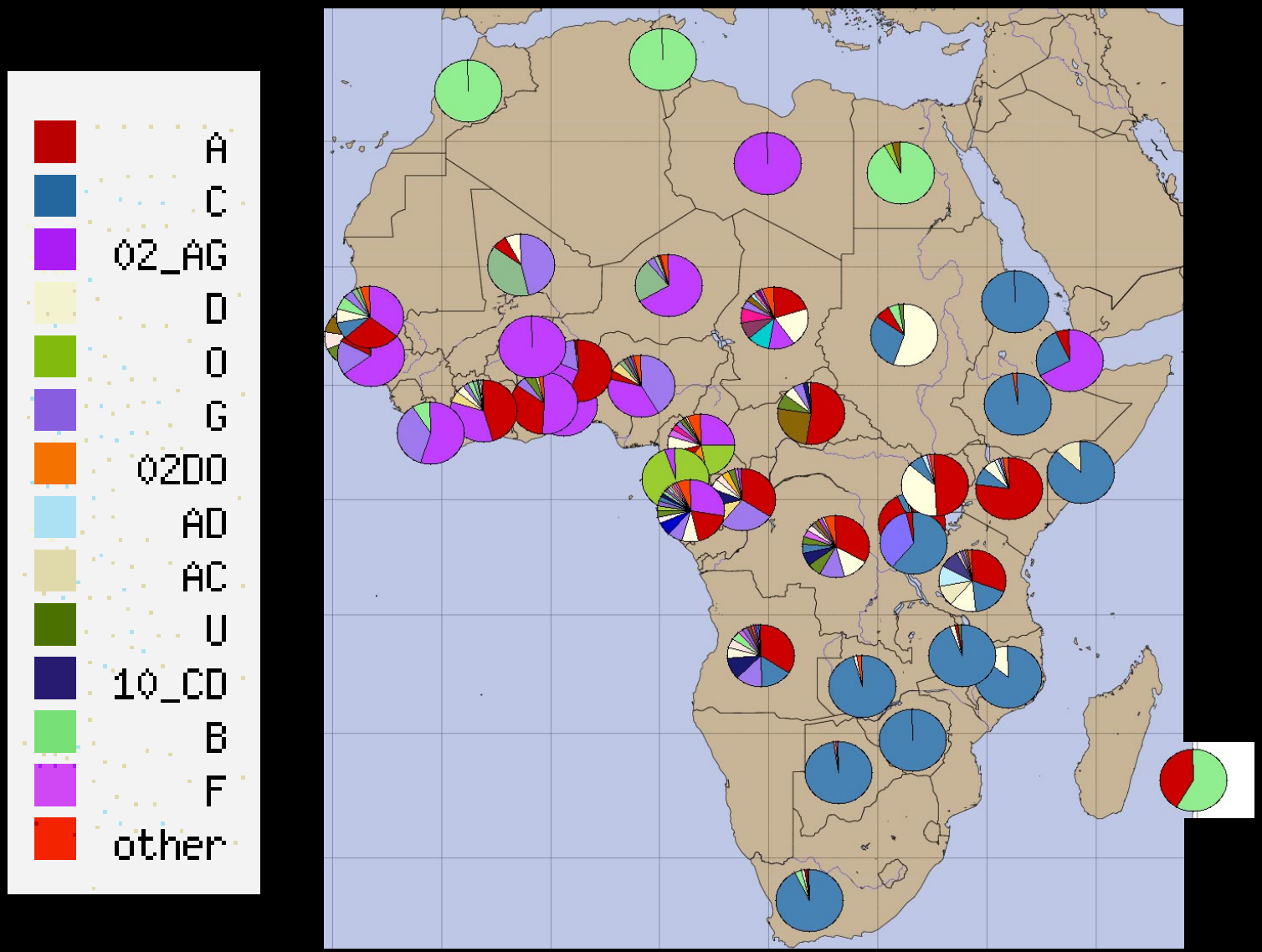
Global distribution of HIV-1 subtypes

Subtype	Global predominance	Main geographical distribution
A	High	Eastern Africa, Eastern Europe, Central Asia
B	High	Americas, Western Europe, Australia, Japan
C	High	South & Eastern Africa, India, China, Nepal
D	High	Eastern Africa
F	Low	South America, Central Africa, Eastern Europe
G	Low	Central Africa
H	Low	Central Africa
J	Low	Central Africa
K	Low	Central Africa
CRF01_AE	High	South-East Asia
CRF02_AG	High	West & Central Africa

Epidemic patterns of HIV-1 subtypes

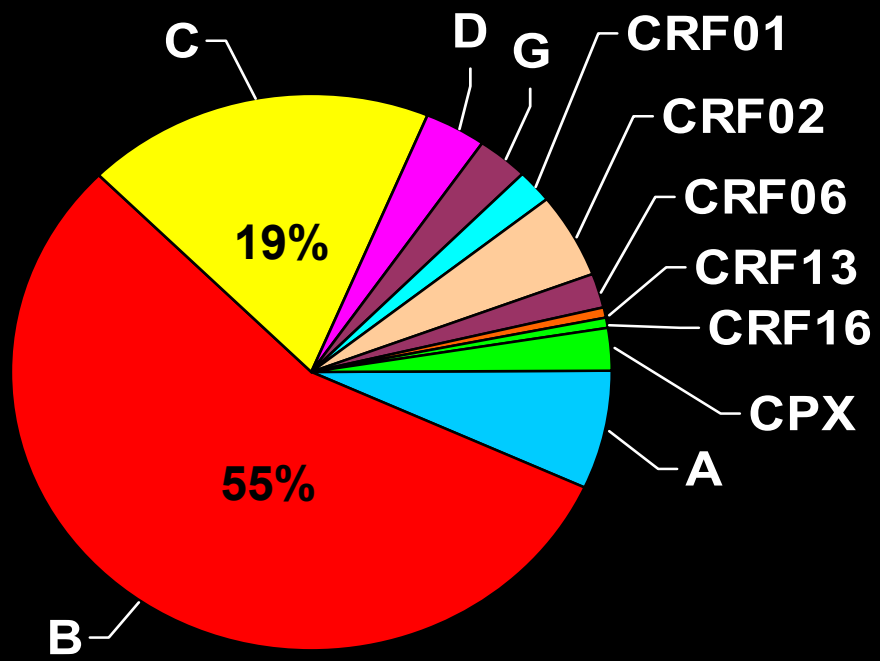


Los Alamos, 2006


A
C
02_AG
D
O
G
02DO
AD
AC
U
10_CD
B
F
other

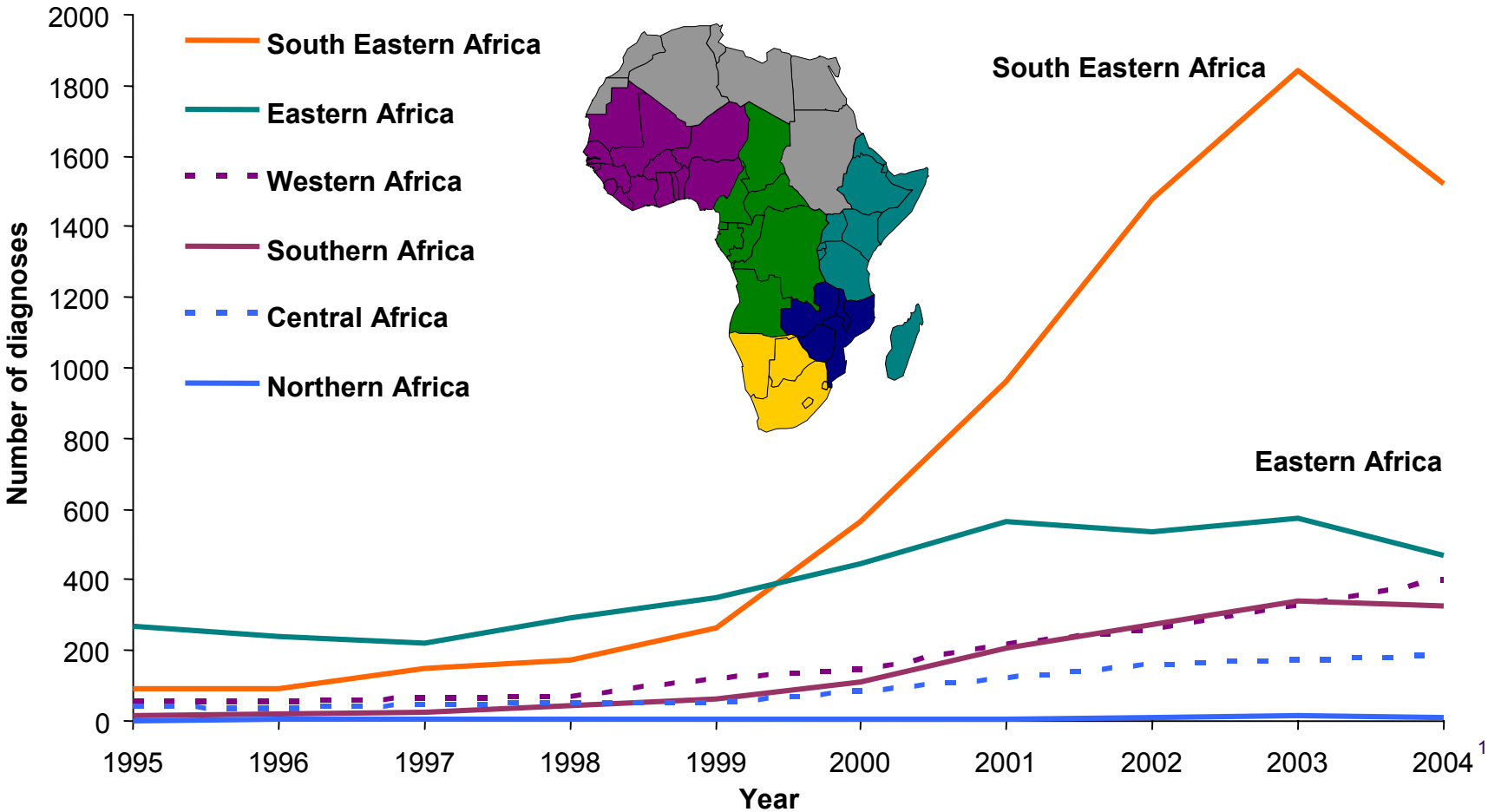
Subtypes reported from the UK

Distribution of HIV-1 *pol* subtypes among newly diagnosed HIV-infected patients *RFH*



Garcia, BHIVA 2006

Probable region of infection for heterosexual HIV infections diagnosed in the UK but probably acquired in Africa



[1]Numbers will rise for recent years, as further reports are received.

Data source: HIV/AIDS diagnosis reports, England, Wales and Northern Ireland

Characteristics of patients infected with B or non-B subtypes at the RFH

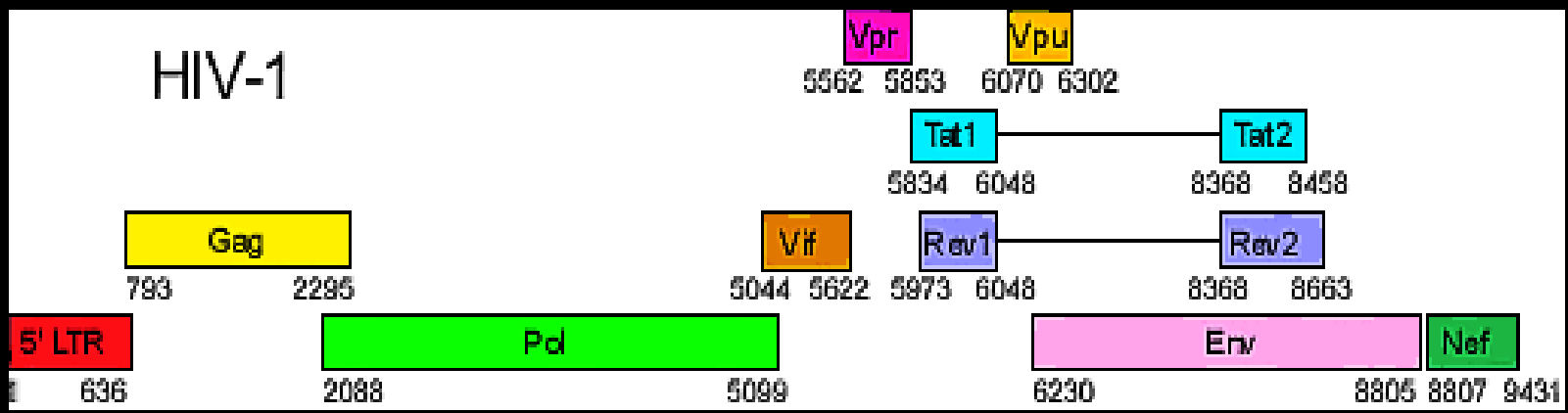
Subtype B	Subtype non-B
95% males	59% females
83% white	69% black-African
89% MSM	92% heterosexual
Median CD4 395	Median CD4 198
4% HCV+	1% HCV+
0% HBsAg+	7% HBsAg+
15% HBcAb+	39% HBcAb+

2/100 (2%) recently diagnosed MSM of white ethnicity infected with non-B subtypes (CRF01, CRF06)

Garcia, BHIVA 2006

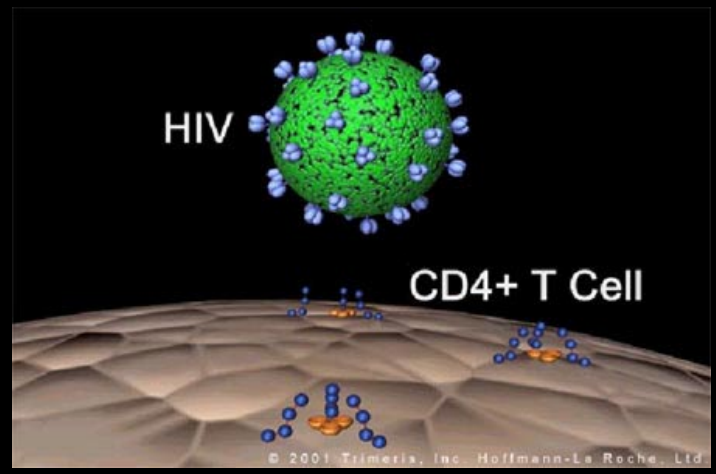
How HIV-1 subtypes differ

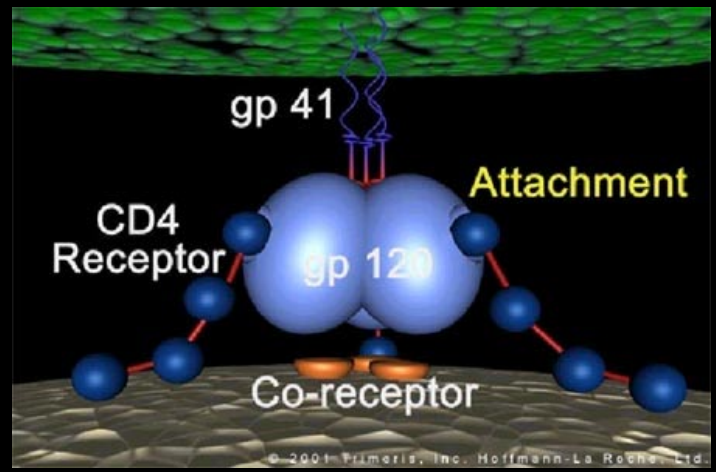
- Sequence of structural genes *env*, *gag*, *pol*
- Sequence of accessory and regulatory genes including *Nef*, *Tat*, *Rev, VPU*
- LTR, transcriptional promoters, response to transcriptional factors
- ➢ Can influence cellular tropism and kinetics of virus replication



Subtype-related features

- Replicative efficiency *in vitro*[1]
  - A, B, D, CRFAE > subtype C > HIV-2 > Group 0
  - Related to gp120 avidity for binding CD4/CCR5
- Length of *env* V1-V2 loop sequences and potential N-linked glycosylation sites n.[2]
  - ↓ in subtypes A and C
  - Related to viral load set point
  - Possible effect on neutralising antibody response
- Co-receptor tropism
  - R5 phenotype predominant in subtypes A and C
  - X4 phenotype predominant in subtype D and BG recombinants[4]





[1]Arien, J Virol 2005; [2]Marozsan, J Virol 2005; [3] Chohan, J Virol 2005; [4]Perez-Alvarez, 3rd IAS 2005

CXCR4 co-receptor use in non-B subtypes

- Tropism for CXCR4 compared among 70 samples obtained from ART-naïve Ugandan women enrolled in HIVNET 012, and 258 other unrelated non-subtype B samples (disease stage and treatment history unknown)

	Viruses using CXCR4 by subtype					
HIV-1 subtype	***A***	***C***	***D***	***F***	***CRFAE***	***G***
HIVNET 012	**0/41 (0%)**		**10/26 (38%)**			
Other samples	**10/48 (21%)**	**7/77 (9%)**	**25/39 (64%)**	**3/18 (17%)**	**9/49 (18%)**	**3/27 (11%)**

Huang, 13th CROI 2006

Subtype-related features

- Subtype C and CRFAE infect and replicate more efficiently in Langerhans cells than subtype B
- Subtype C shows greater propensity for *in utero* vertical transmission[1] and higher levels of shedding in the genital tract than subtypes A or D[2]
- CRFAG is associated with higher plasma viral load during the first 4 months and in the asymptomatic phase of infection[3,4]

[1]Renjifo, AIDS 2004; [2]John-Stewart, JID 2005; [3]Sarr JID 2005; [4]Fischetti, AIDS 2004

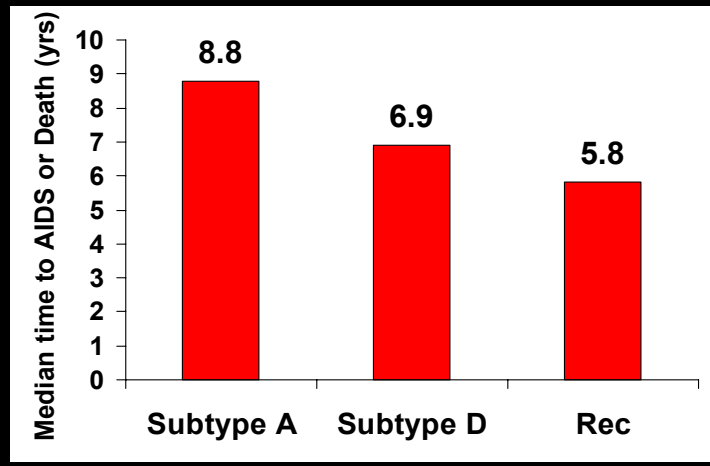
The impact of HIV-1 subtype on disease progression

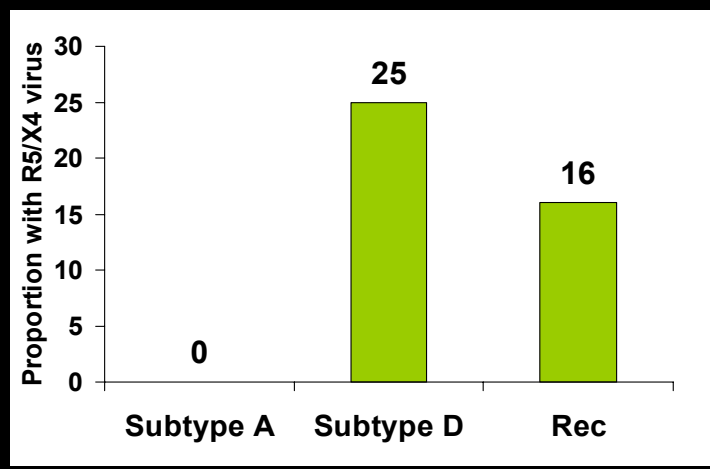
- Retrospective study (n=340)
- Newly infected individuals identified in 1994-2001 in Rakai, Uganda
- Median age and VL did not differ by subtype

Cox Regression Analysis of AIDS or Death

Subtype	HR	95% CI	*P*
A	1.0	1.0	-
D	2.89	1.03-8.07	*0.043*
Rec	4.88	1.45-13.1	*0.005*
VL	1.83	1.32-2.67	*0.001*

Gender, age, multiple infection NS

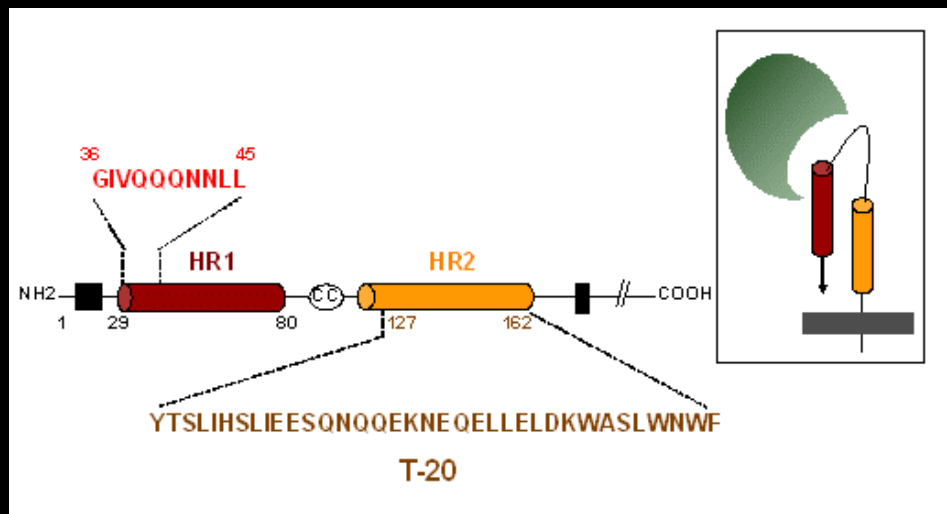




Laeyendecker, 13th CROI 2006

HIV-1 subtypes and drug resistance
- Entry inhibitors -

- Natural resistance to BMS-378806 (inhibits gp120/CD4 interaction) can occur with subtype C and CRFAE[1]
- No natural resistance to T20 observed so far [subtype C, CRFAE, CRFAG][2-4]
  - HR1 variability at positions not known to be associated with resistance[3]
  - High variability in HR2[3]
  - Subtype C: enhanced susceptibility *in vitro*[5]



[1]*Moore, AIDS 2004;* [2]*Aghokeng, AIDS Res Hum Retroviruses 2005;*
[3]*Cilliers, AIDS Res Hum Retroviruses 2004;* [4]*Fleury, Antivir Ther 2005;* [5]*Marozsan, J Virol 2005*

HIV-1 subtypes and drug resistance - RT and Protease inhibitors -

- Naturally occurring, major resistance mutations not common in non-B subtypes
- Subtype B *vs* subtypes A-G, CRFAE and CRFAG: 48% RT positions and 53% PR positions polymorphic in >1% of untreated persons
  - Some polymorphisms are consensus sequences in certain subtypes
  - Several polymorphisms are secondary resistance mutations in subtype B
- ➢ Impact on natural drug susceptibility?
- ➢ Impact on genetic barrier to resistance?

Consensus		
Gene	**Position**	**Subtype**
RT	**A98S**	**G**
	V179I	**A**
	K238R	**CRFAE**
PR	**K20I**	**G, CRFAE**
	M36I	**A, C, D, F, G, CRFAE, CRFAG**
	V82I	**G**
	L89M	**C**
	I93L	**C**

In vitro drug susceptibility:

Some non-B strains (A, C, G, CRFAE, CRFAG) show reduced susceptibility to ABC, NNRTIs, PIs [ATV, NFV, LPV]

Transmitted resistance in sub-Saharan Africa

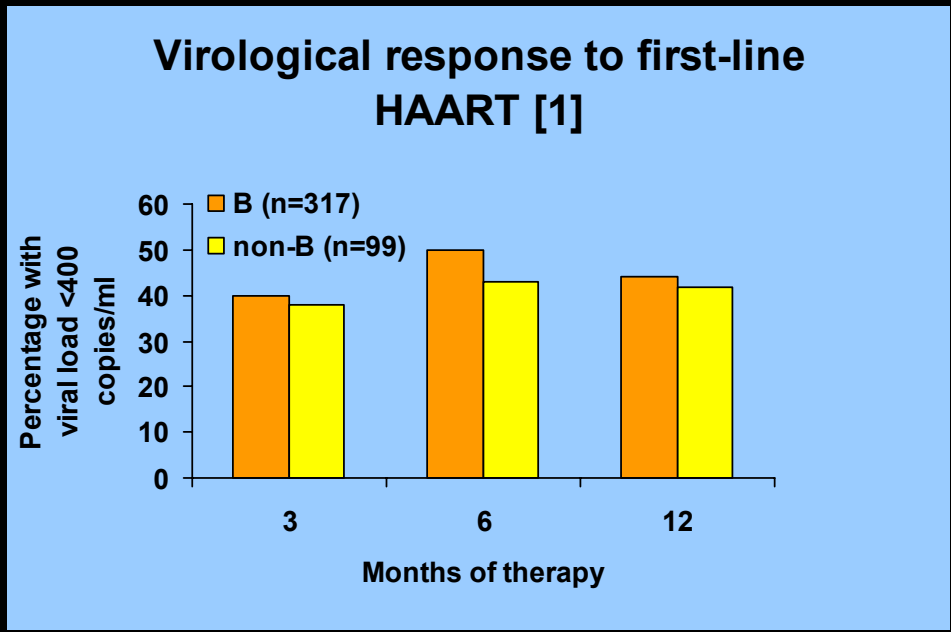
Year	Place	No	Study group (age)	Subtype	Prevalence
2001 2004	Yaoundé, Cameroon	96	Pregnant women diagnosed <12 mo	AG >58%	**Any 2.1%** NRTI 1.0% PI 1.0%
2001 2002	Yaoundé, Cameroon	102	Recently diagnosed blood donors & hospital attendees	AG 59%	**Any 7.8%** NRTI 2.9% NNRTI 2.0% PI 2.9%
2004	Western Cameroon	54	Antenatal, STD or Health Centres attendees Clonal proviral DNA	AG 93%	**Any 14.8%** NRTI 3.7% NNRTI 5.5% PI 7.4%
2003	Burkina Faso	97	Recent diagnoses attending hospitals & treatment centres	AG 49% O6 47%	**Any 8.3%** NRTI 2.1% NNRTI 4.1% PI 2.1%
2002	DRC	70	Subset of sentinel population with various subtypes	Multiple	**Any 4.3%** NNRTI 1.4% PI 2.9%

Geretti AM, Current Opinions in Infectious Diseases, in press

- Characterisation of the genetic diversity of HIV-1 strains is an important pre-requisite to aid the development of appropriate guidelines for surveying transmitted drug resistance

Responses to HAART

- Virological responses to first-line HAART similar in patients with B or non-B subtypes over 12[1] and 24 months[2]
- In subtype C, viral load kinetics after starting NNRTI-based HAART are similar to those seen in subtype B, with excellent virological and immunological responses after 3 months of therapy[3]
- High baseline viral load and use of NRTI-only regimens prolong the time to undetectable viral load regardless of subtype[1]
- Ethnicity (rather than subtype) may influence responses[4]
- Poorer CD4 recovery in subtype A?[2]



[1]Bocket, Antiv Ther 2005; [2]De Wit, AIDS 2004
[3]Cassol, JID 2005; [4]Monno, J Med Virol 2005

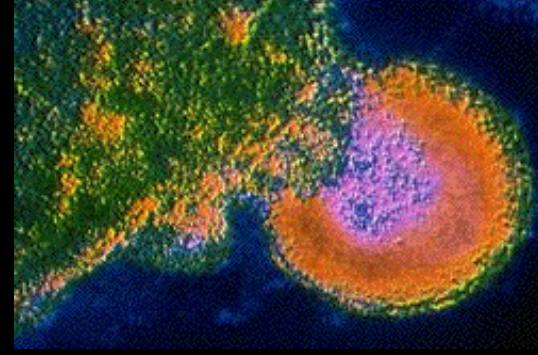
HIV-1 subtypes and resistance pathways

- The major resistance mutations identified in subtype B are also involved in resistance in the most prevalent non-B subtypes
- Some mutations appear to differ in frequency:
  - EFV: V106M common in subtype C and CRFAE
    uncommon in subtype B
  - NFV: L90M predominant in subtypes C, G and CRFAE
    D30N predominant in subtype B
  - PIs: V82A more common in subtype B and I82M/T/S in subtype G
- Therapy-associated changes in RT and PR that have not been recognised as resistance mutations occur in all subtypes
  - Some of these (e.g. RT 98) more frequent in certain subtypes
- There are at least 6 mutations with unknown effects on drug susceptibility that appear to be associated with therapy in at least one non-B subtype but not in subtype B
  - RT 102 (C)
  - PR 6 and 64 (C), 15 (CRFAG), 19 (F), 37 (A) and 64 (CRFAE)

Other clinical implications of subtype-related variability

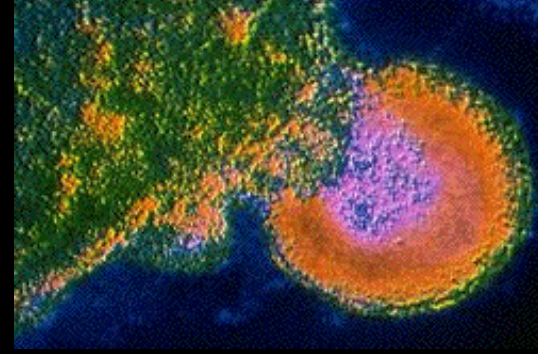
- Performance of viral load assays
- Performance of genotypic and phenotypic assay

Summary and implications for clinical practice-1

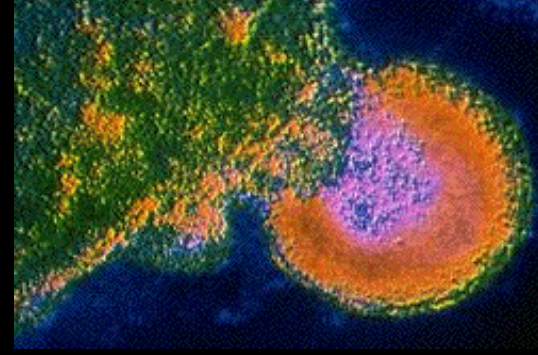


- HIV-1 molecular epidemiology complex and evolving
- Emergence of new variants reflects HIV-1 prevalence, subtype epidemiology and risk behaviour patterns in different geographical areas
- Genetic differences among HIV-1 variants can influence biological properties and translate into different transmission and pathogenic potential
- *Pending further evidence, plasma viral load, CD4 count and remain the important predictors of disease outcome, regardless of the infecting subtype*

Summary and implications for clinical practice -2



- Antiretroviral drugs developed using B subtypes
- Important to determine whether subtype-related sequence variability impacts on natural drug susceptibility
- Responses to current HAART regimens do not appear to differ significantly among common subtypes
- *Current regimens can be used reliably to treat patients with both B and common non-B subtypes*
- Subtype-related variability influences resistance pathways
  - Major resistance mutations similar
- *Resistance interpretation algorithms give adequate guidance*



- *The limitations of current evidence should be acknowledged and instigate ongoing surveillance*

Thank you