Immunization in HIV-infected Adults

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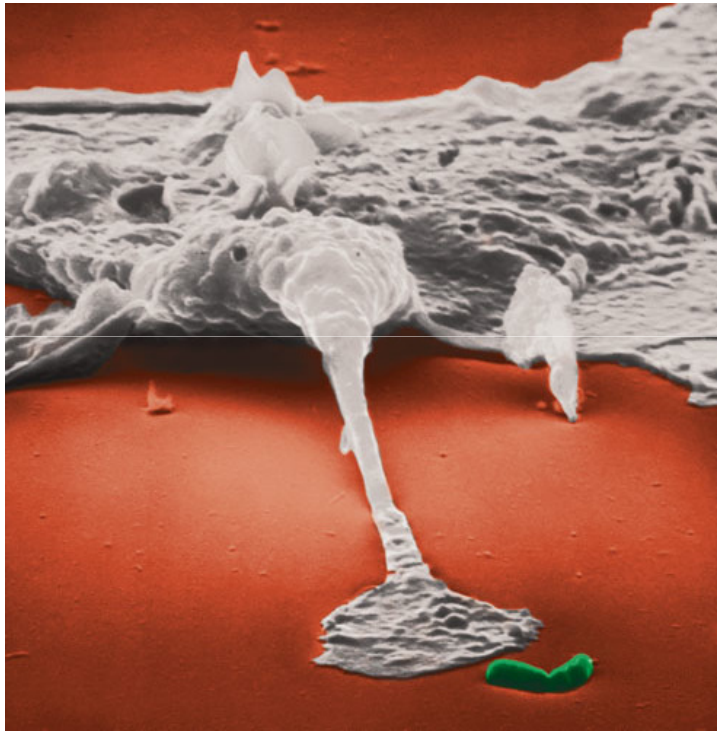
Outline of the talk

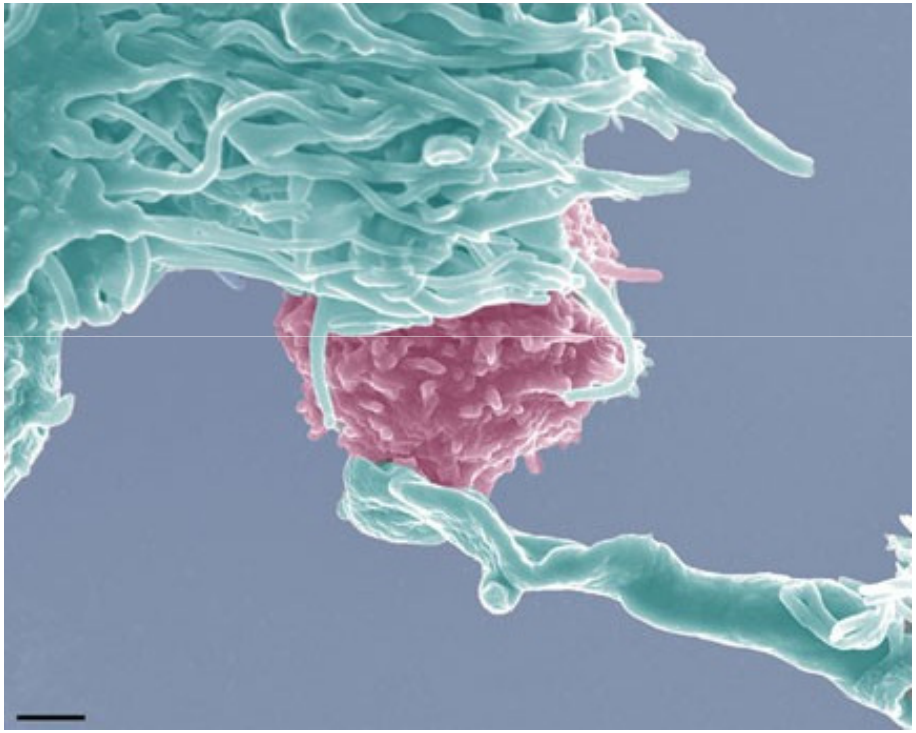
- Vaccine type as a determinant of response
- Why does HIV present a problem?
- Principles for immunization of adults with HIV
- Missed opportunities to vaccinate

Types of Vaccine

Live attenuated	Inactivated	Toxoid / Other	Polysaccharide
BCG	Hepatitis A	Diphtheria	Hib
Influenza (intranasal)	Influenza	Hepatitis B (protein)	Hib-conjugate
Measles	Pertussis (Whole cell)	Human Papillomavirus (VLP)	Meningococcal
Mumps	Polio (inactivated, IPV)	Pertussis (acellular)	Meningococcal-conjugate
Rubella	Rabies	Tetanus	Pneumococcal (PPV)
Polio (Oral)			Pneumococcal-conjugate (PCV)
Rotavirus			Typhoid
Varicella			
Yellow Fever			

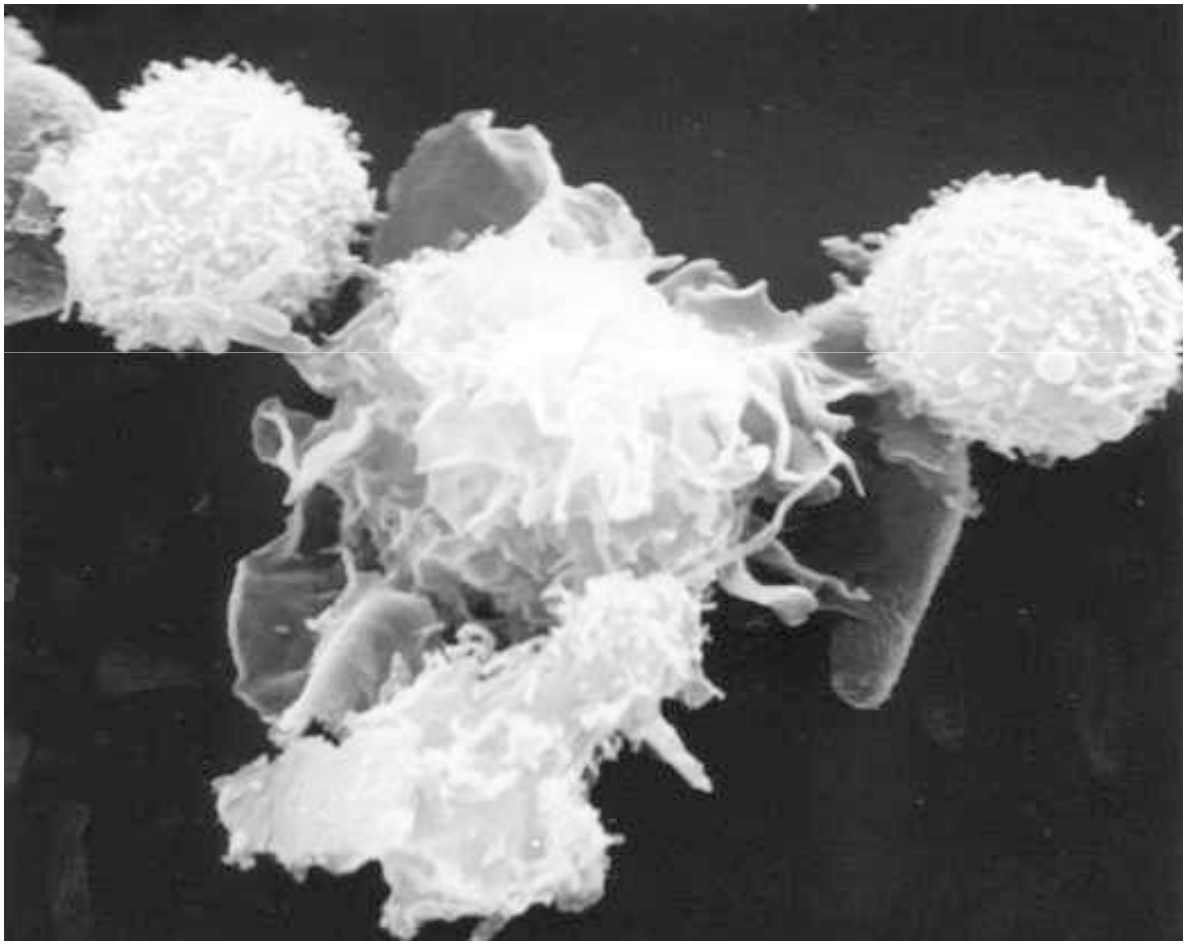
T-dependent antibody production





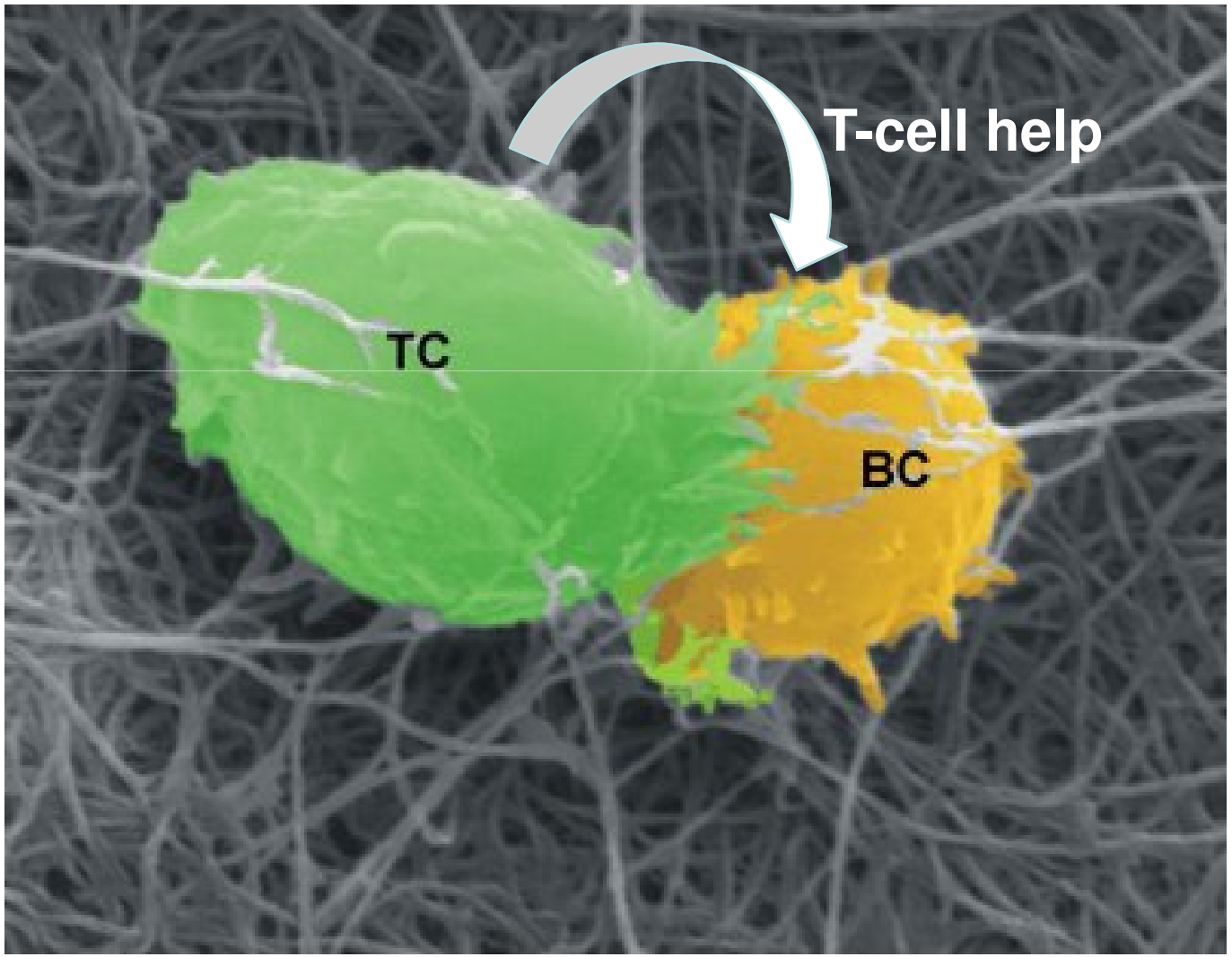
DC migration to
Regional LN

T-dependent antibody production

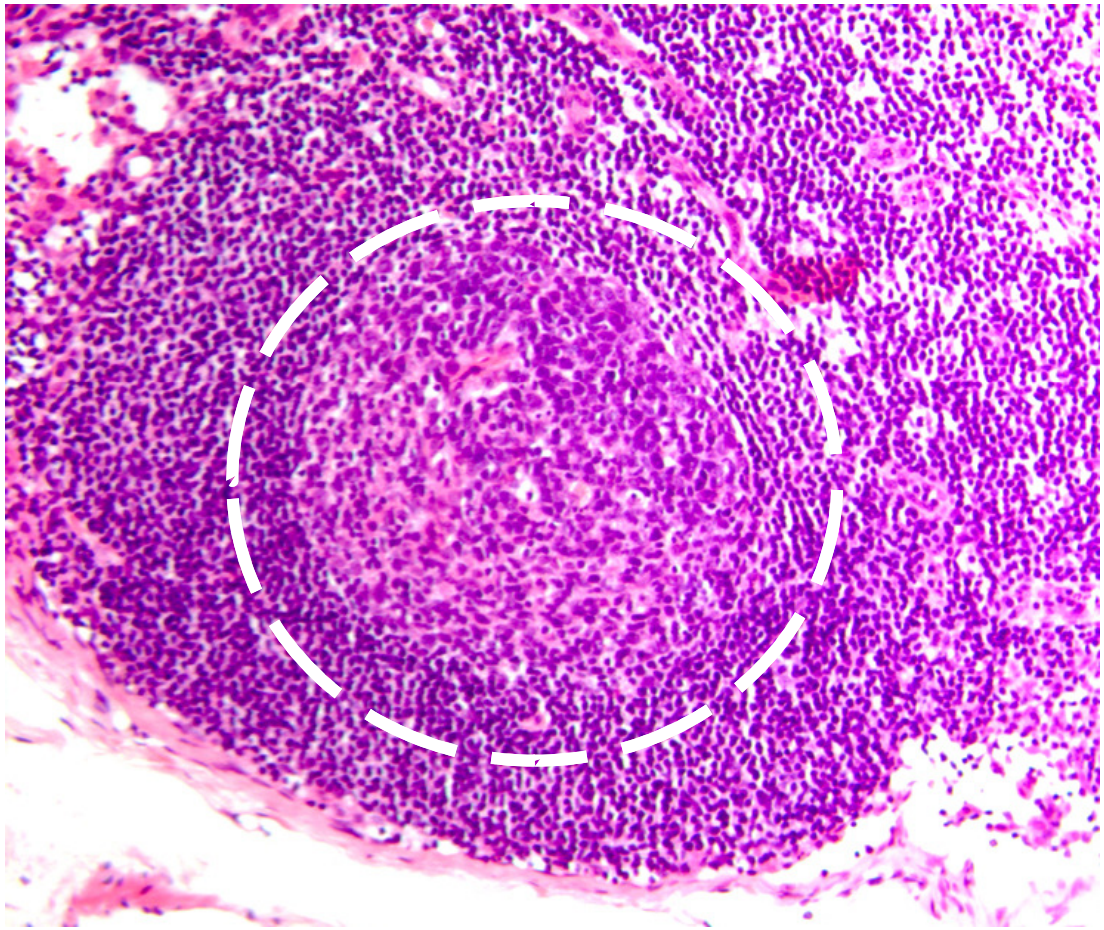


Amplification of the Ag-specific T-cell response

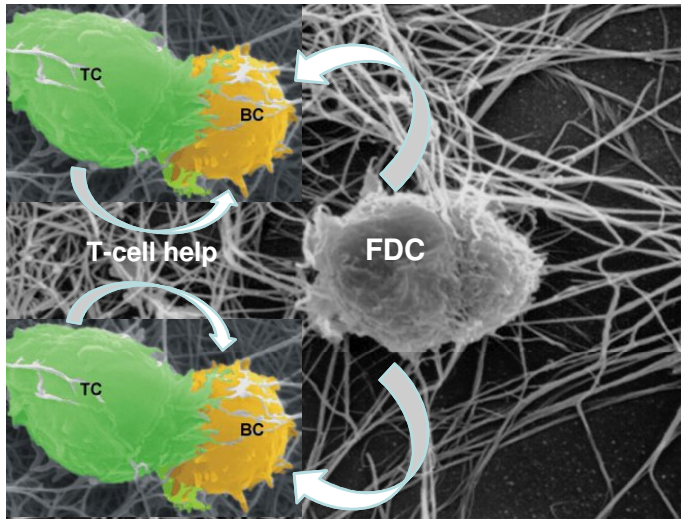
T-dependent antibody production

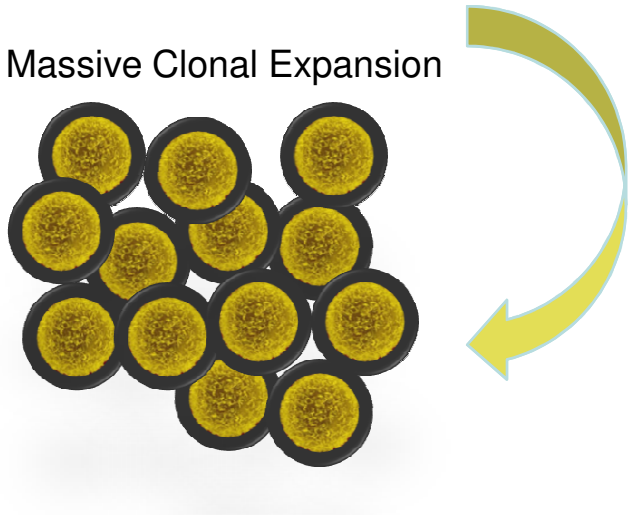


T-dependent antibody production

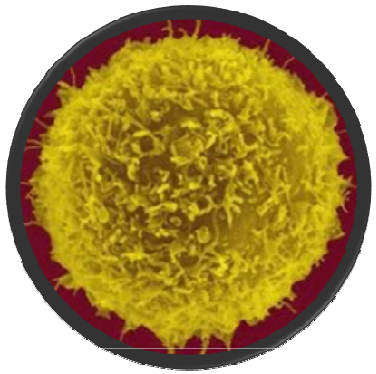


Lymph Node Germinal Centre

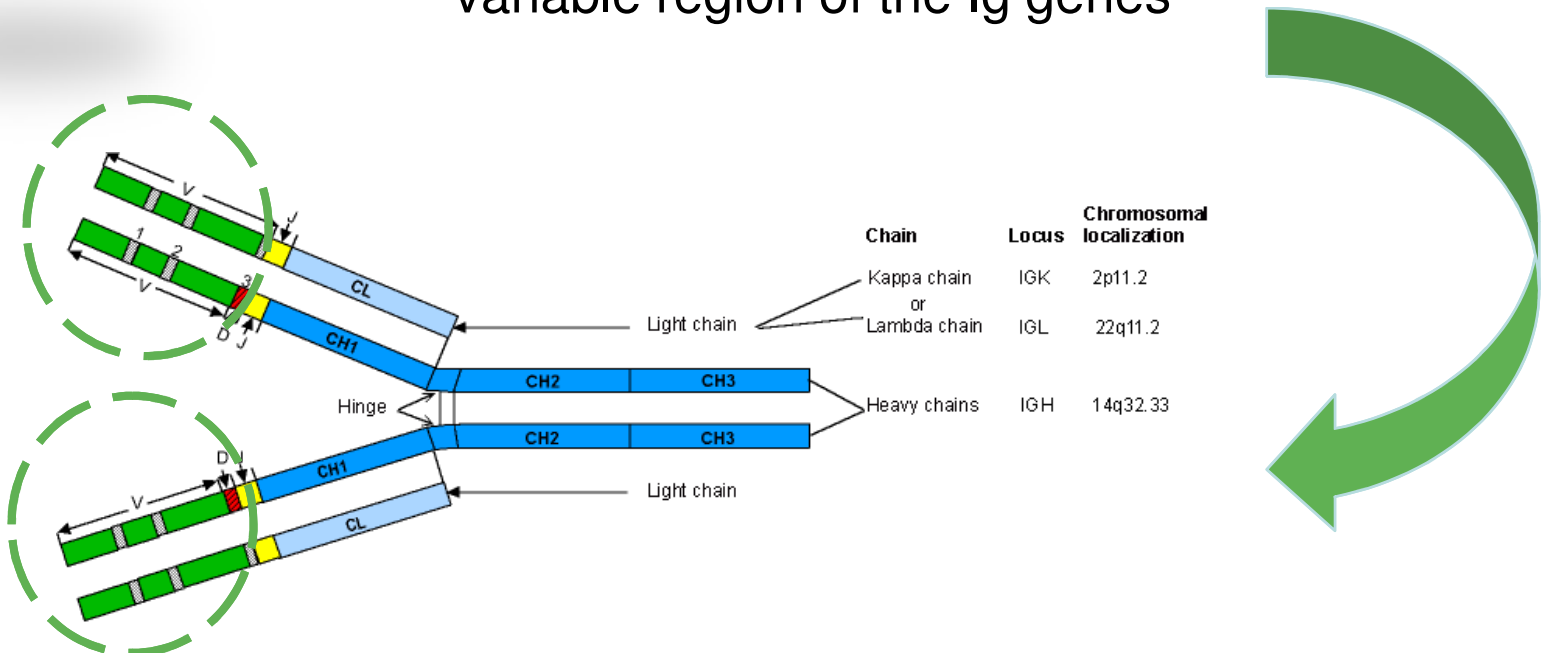




T-dependent antibody production

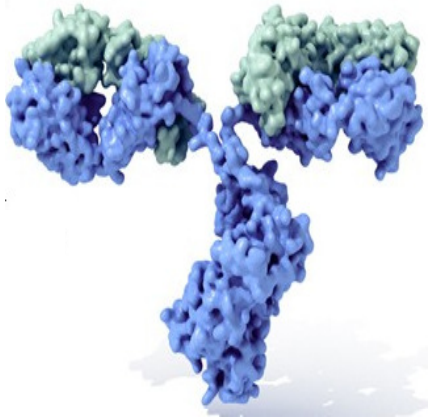


Massive Somatic Mutation within variable region of the Ig genes

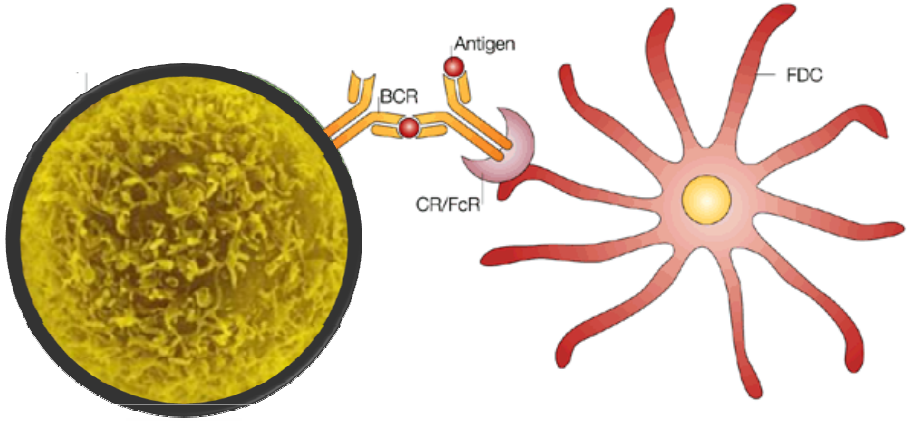


Chain	Locus	Chromosomal localization
Kappa chain	IGK	2p11.2
or		
Lambda chain	IGL	22q11.2
Heavy chains	IGH	14q32.33

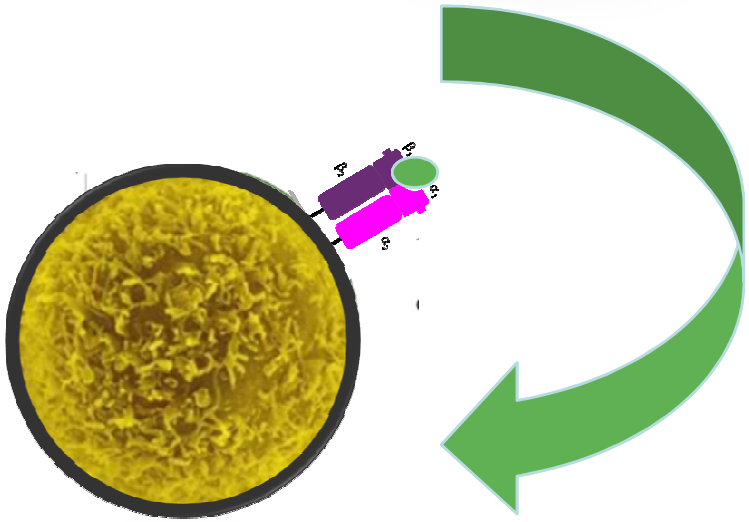
T-dependent antibody production



Generation of a minority of Ig
With INCREASED affinity for Ag

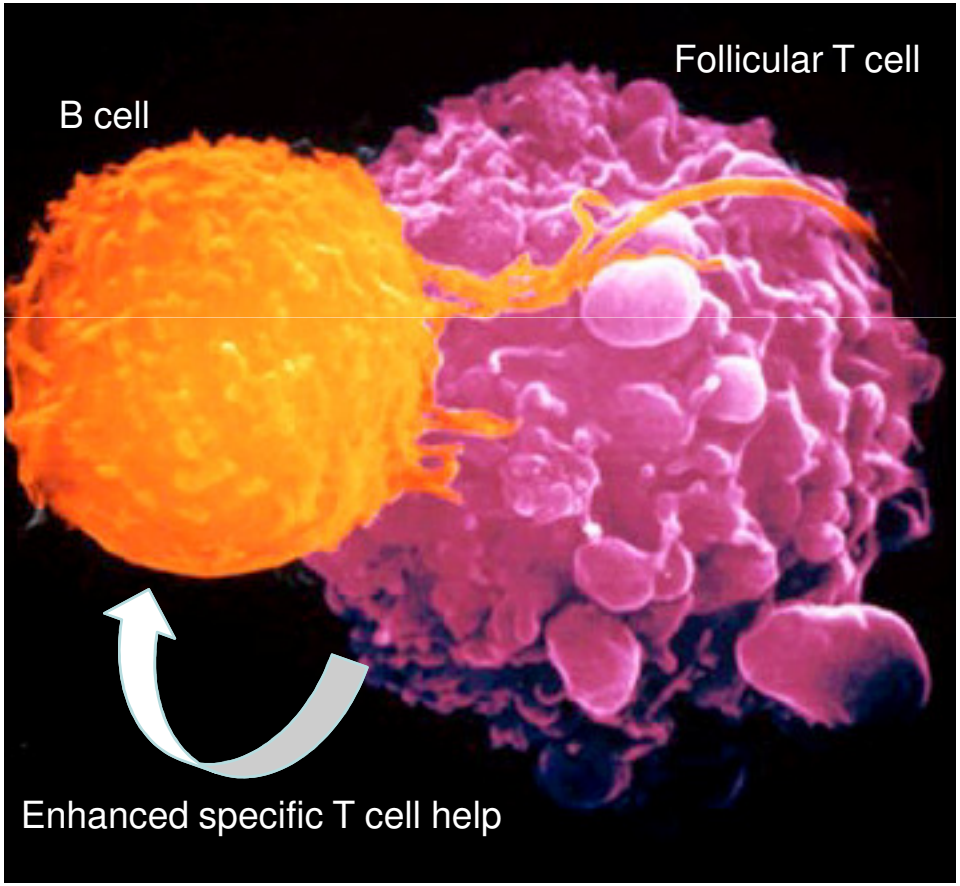


B cells efficiently compete for binding
to small amounts of vaccine Ag on FDCs



Process vaccine antigens
into small peptides
expressed on B cell surface
with MHC class II

T-dependent antibody production



Selection, proliferation & survival of B cells with the highest Ag-specific affinity

Differentiation signals drive plasma cell development & secretion of **specific antibodies** or memory B cells

HIV-induced immune suppression reduces vaccine responses

- Reduced CD4 T cell help
- Reduced Dendritic cell responses
- Reduced B cell numbers and function
- Reduced antibody production

Principles of immunization in HIV-infected adults

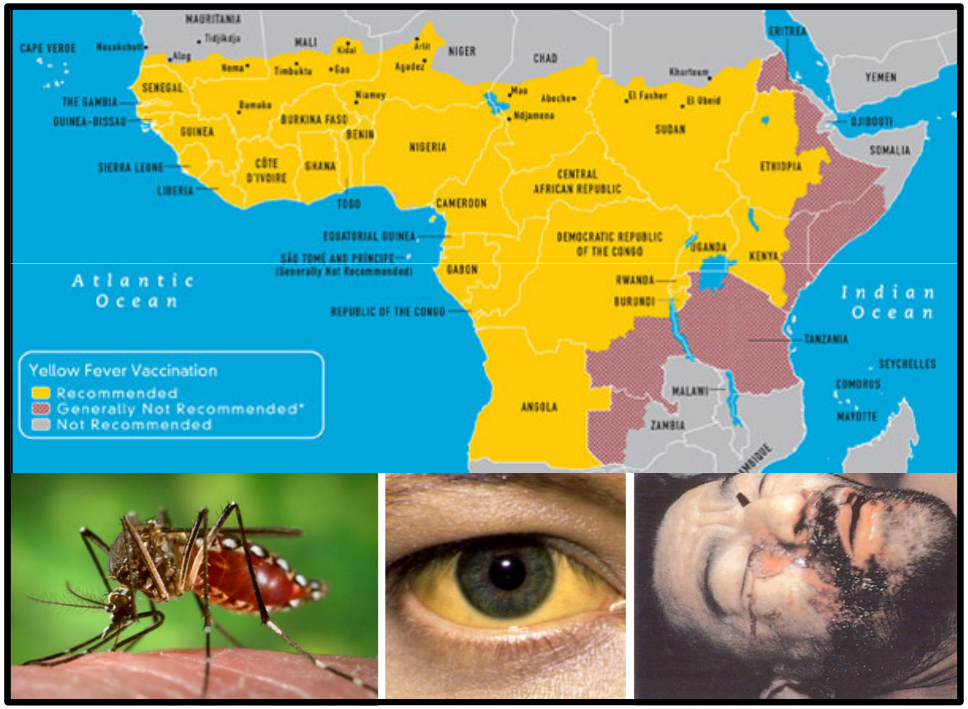
- Vaccination is associated with HIV viral load blip and transient reduction in CD4 count
- Avoid live vaccines if CD4 count < 200 cells/mm^3

MMR Vaccination

- Indicated for measles IgG seronegative persons
- Avoid pregnancy for 1 month post-vaccination
- Breast feeding is not contraindicated
- Safe for household contacts
- Contraindicated CD4 <200

AIDS 2004;18: 826-7. Vaccine 2005; 23: 3256-3263

Yellow Fever Vaccination

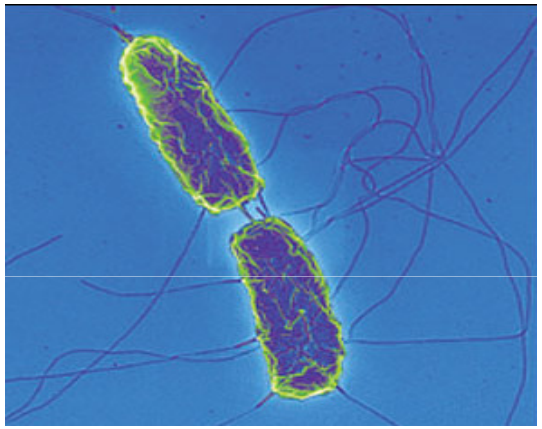


- Increased neurotropic and viscerotropic adverse disease events in persons with CD4 <200
- Well tolerated with seroconversion rate ~ 85% in persons with CD4 >200
- Transient drop in CD4 count and rise in HIV viral load
- Adverse event reporting increases > 60 years age (x6)

AIDS 2004;18:826-7. Vaccine 2005;23:3256-3263

Other Live Vaccines

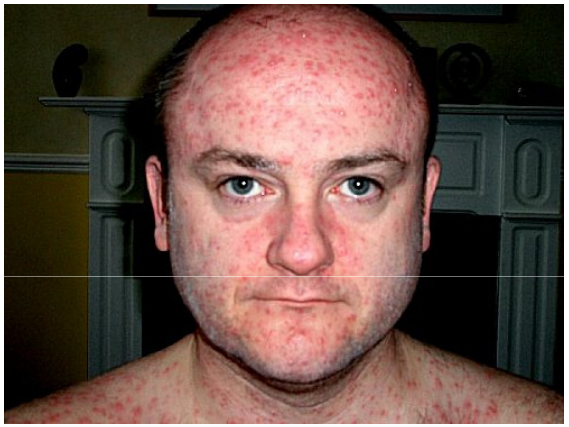
Ty21a Oral Typhoid



Contraindicated

Use inactivated Typhoid ViCPS

Varicella Zoster



Contraindicated if CD4 <200 cells/mm^3

Indicated in clients if CD4 >200 cells/mm^3

Avoid pregnancy for 1 month

Poliomyelitis, oral

Contraindicated

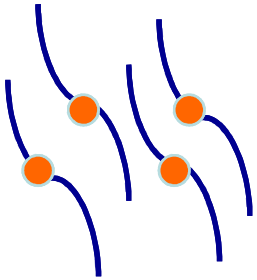
Use inactivated vaccine instead

Contraindicated in household contacts

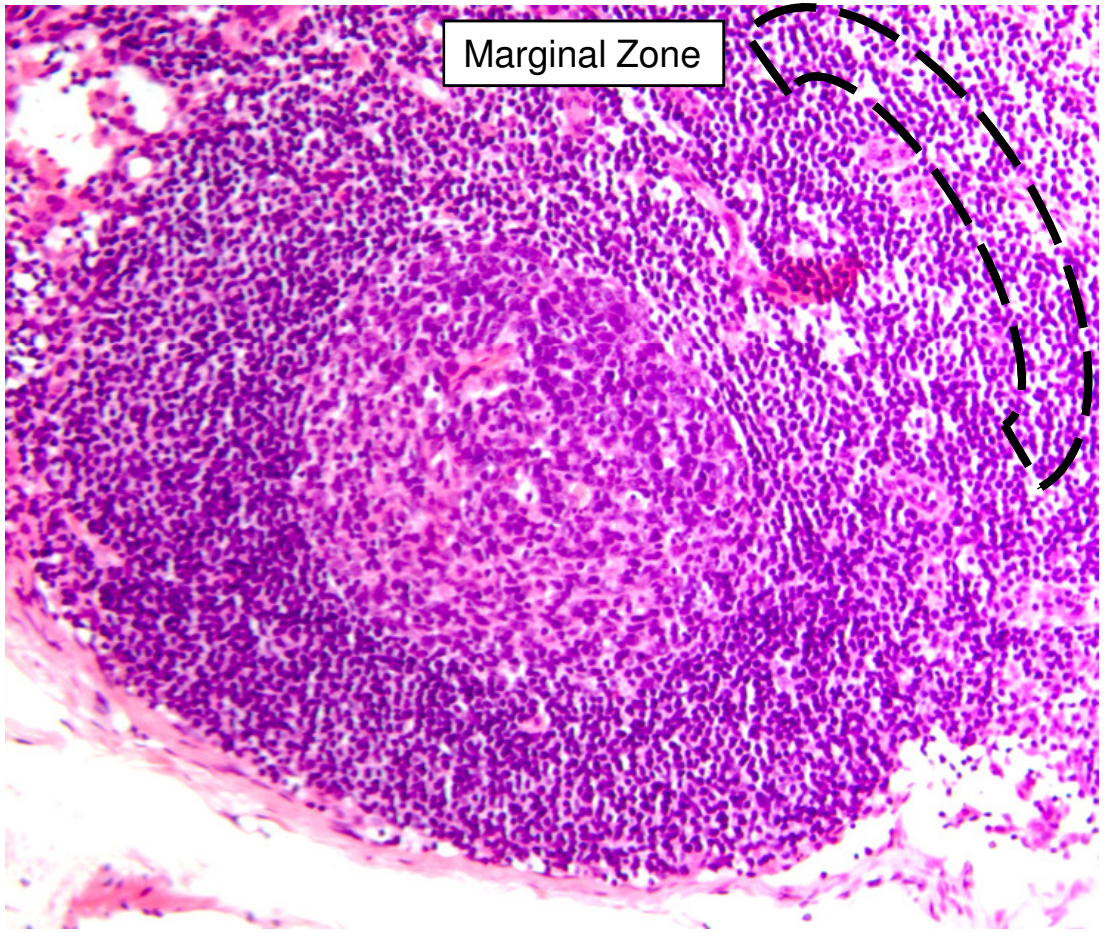
Principles of immunization in HIV-infected adults

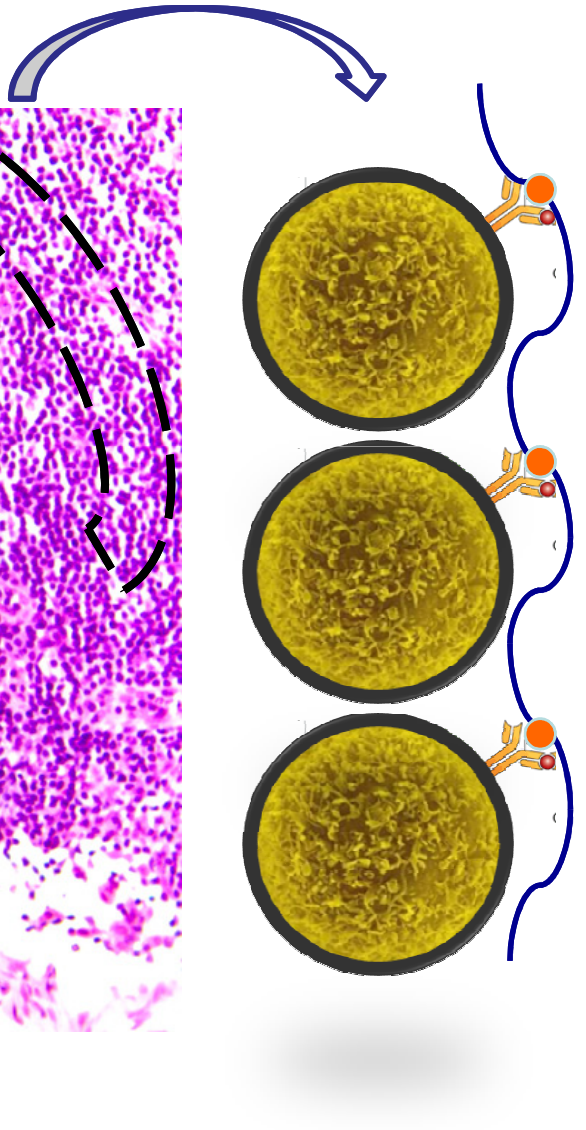
- Vaccination is associated with HIV viral load blip and transient reduction in CD4 count
- Avoid live vaccines if CD4 count < 200 cells/mm^3
- Polysaccharide vaccines elicit poor antibody responses

T-independent antibody production

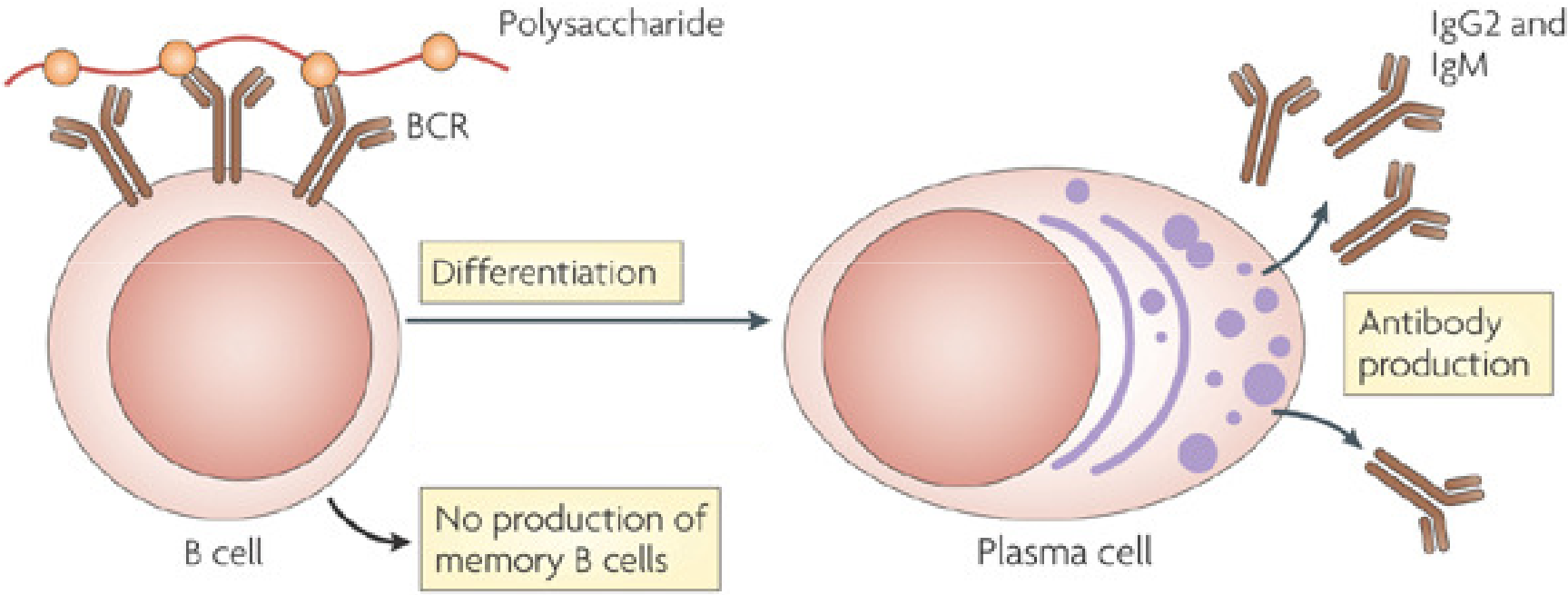


Bacterial
Polysaccharide
Antigens





T-independent antibody production

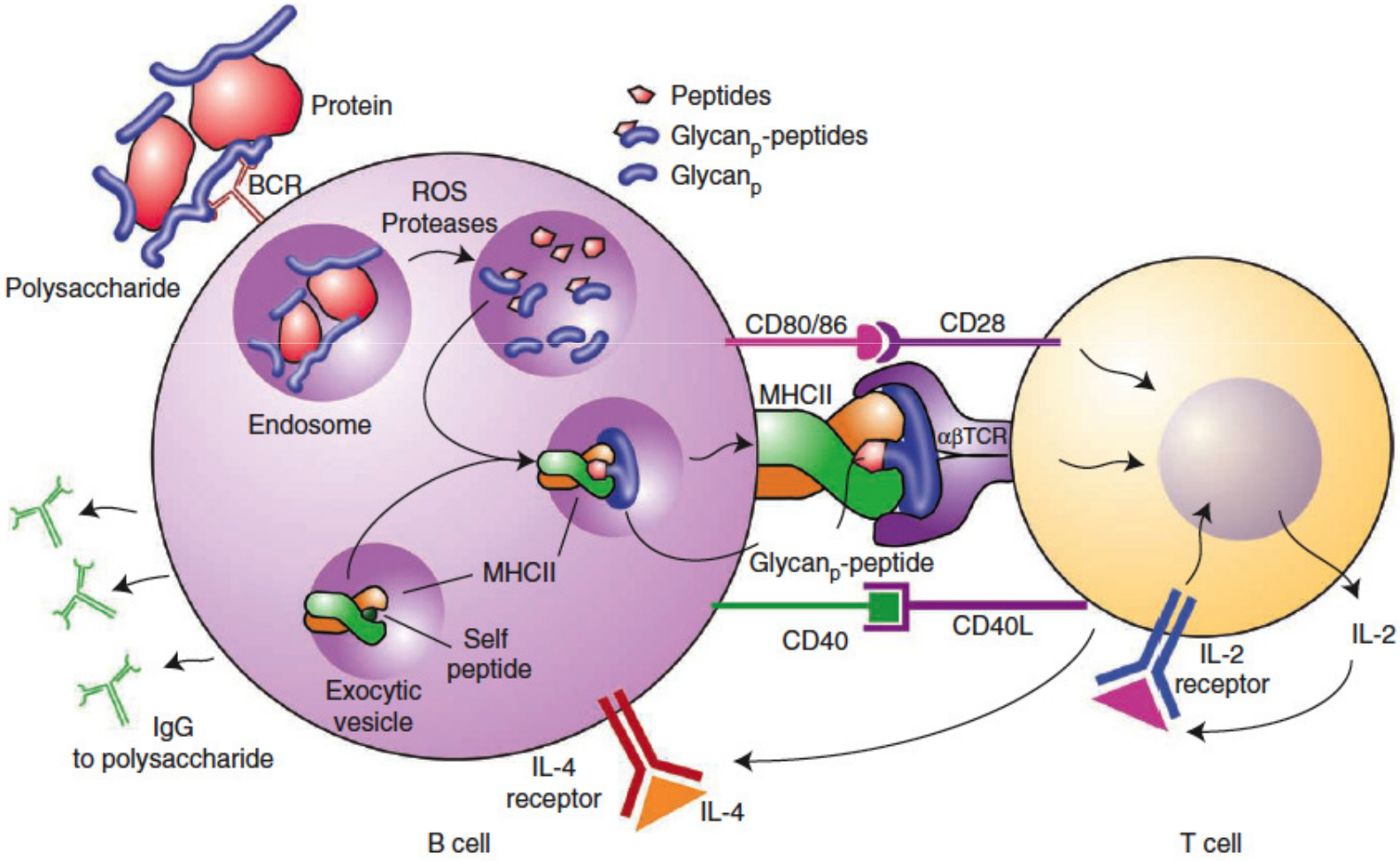


Non-mutated, low-affinity ‘germline’ Abs

Move towards red pulp of spleen – apoptosis

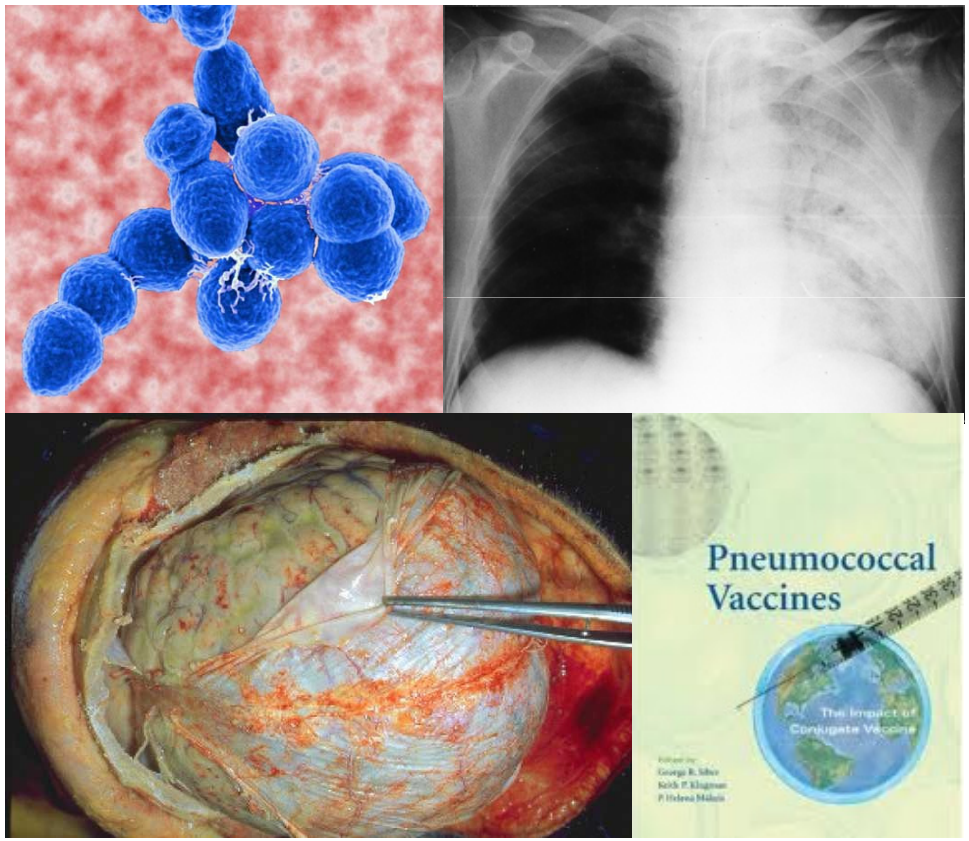
Short-lived response

Conjugating polysaccharide with protein induces a T-dependent antibody response



Avci et al. Nature Medicine 2011;17(12):1602-10

Pneumococcal Vaccines



- 10-300 x more susceptible to invasive pneumococcal disease (IPD)
- 25% risk of recurrent IPD within 12 months
- 2-3 fold reduction IPD in persons on ART, but still ~35 x greater than general population

Hefferman et al. JID 2005;191:2038-45. Gilks et al. Lancet 1996;347:718-23

Pneumococcal Polysaccharide Vaccine (PPV-23)

- HIV-infected adults with CD4 >200 cells/mm^3 as soon as possible after diagnosis
- Elicits modest antibody responses, lower than healthy controls
- Ugandan RCT
  - increase pneumonia in 6-month period in those not on ART
  - 16% overall reduction all cause mortality
- Meta-analysis – marked heterogeneity in efficacy with no overall benefit

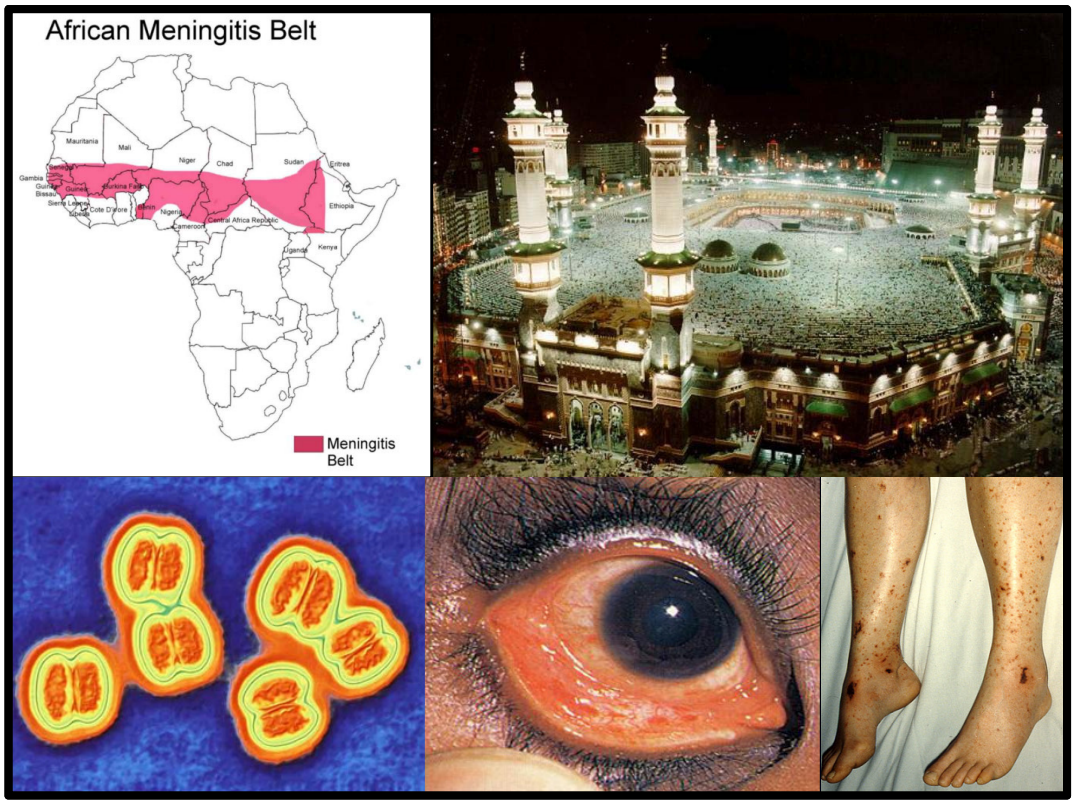
French et al. Lancet 2000;355:2106-11. Pedersen et al. HIV Medicine 2011;12:323-33

Pneumococcal Conjugate Vaccine (PCV-7, PCV-13)

- Greater immunogenicity than PPV
- Low coverage of IPD-causing strains necessitates use of PPV-23 in addition to PCV
- More durable antibody response on ART
- RCT of PCV-7 vs placebo for reduction of IPD recurrence
  - Vaccine efficacy reduced from 85% in year 1 to 25% in year 2
  - Efficacy 88% in CD4 <200 cells/mm^3 group
  - Overall protection regardless of serotype hazard ration 0.76 (95% CI 0.42-1.42)

French N et al. N Engl J Med 2010;362:812-22

Meningococcal Conjugate Vaccine



- Increased severity of *N. meningitidis* infection
- Mandatory vaccine for pilgrims to the Hajj
- Conjugate vaccines target subtypes A,C, Y & W-135
- Quadrivalent Conjugate vaccine safe & efficacious
- Decreased response to serotype C

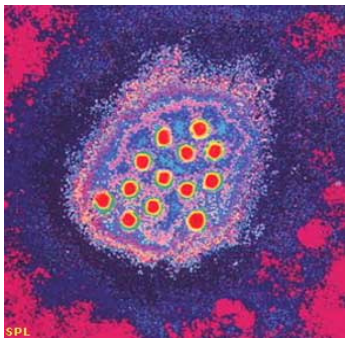
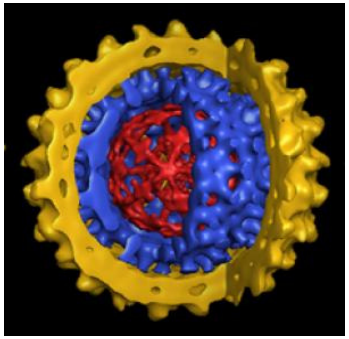
Typhoid Vi Capsular Polysaccharide Vaccine

- HIV increases chance of:
  - fulminant diarrhoea
  - fulminant colitis
  - bacteraemia
  - antibiotic resistance
  - relapsing disease
  - persistent infection
- Serological response decreased in CD4<200

Principles of immunization in HIV-infected adults

- Vaccination is associated with HIV viral load blip and transient reduction in CD4 count
- Avoid live vaccines if CD4 count < 200 cells/mm^3
- Polysaccharide vaccines elicit poor antibody responses
- Extra booster doses are commonly employed but often without hard evidence

Booster doses recommended

Hepatitis A		Safe and well tolerated at all CD4 counts Response rates reduced but good clinical efficacy Some guidelines suggest 3rd dose
Hepatitis B		Standard (0, 1, 6m) or rapid (0, 1, 2 and 12m) HBsAb <10 iu/L — 3 further double-doses HBsAb 10–100 iu/L — 1 additional vaccine dose HBsAb >100 iu/L — Check yearly and boost
Rabies		Considered safe at all CD4 counts 3 x intramuscular doses (0, 7 and 28 days) ± 4th dose if Ab response poor at low CD4 counts

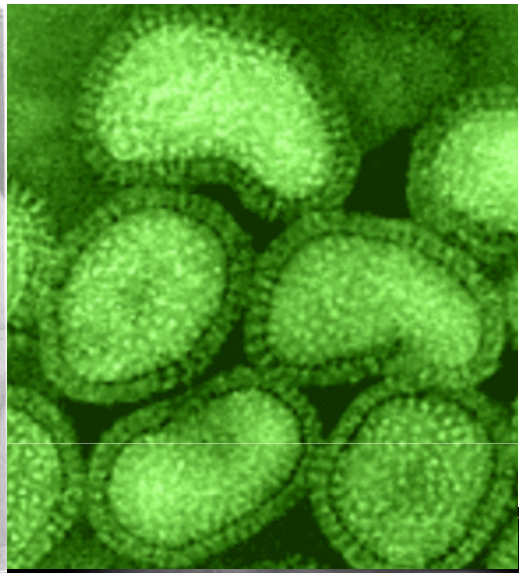
Missed Opportunities

Hepatitis B vaccination

- RCT - Double dose vaccine in CD4 >350 cell/mm^3
  - 69% versus 34% serocoversion rate
- Hepatitis B testing only occurs at ART initiation
- Options for vaccinating HBV seronegatives
  - Continue the staus quo in Southern Africa
  - Vaccinate high risk groups only – IVDU, MSM, Sex care workers, partners of HBsAg positives
  - Universal HBV vaccination for those not yet infected

Fonseca et al. Vaccine 2005;23:2902-8. Mendelson et al. SA J HIV Medicine 2011;Apr; 27-33

Influenza vaccination in HIV



Seasonal influenza and HIV

Pre-ART era

- Higher rates of
  - Hospitalization
  - Secondary bacterial infection
- Prolonged illness
- Increased Mortality

Post ART era

- Reduction in cardiopulmonary admissions by 56%
- Risk still > general population

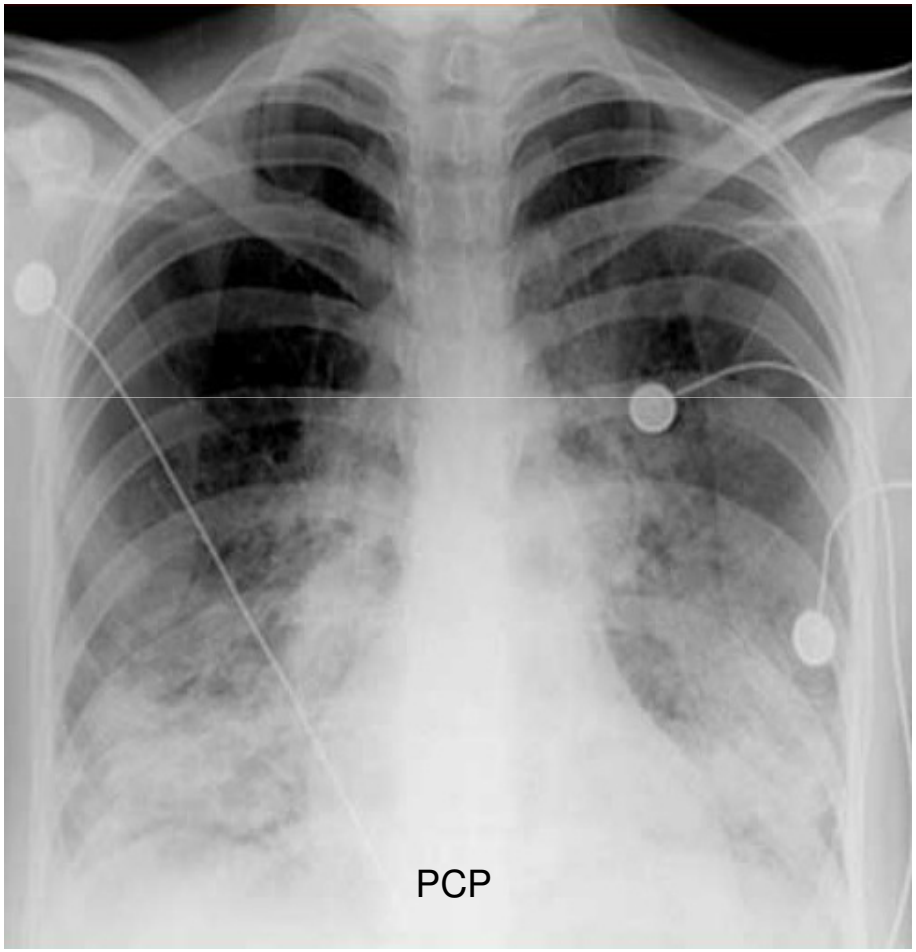
Neuzil et al, JAMA 1999;281:901-7
Madhi et al. J Pediatr 2000;137(1):78-84
Lin et al. Arch Int Med 2001;161 :441-46
Madhi et al. Paed Infect Dis J. 2002;21(4):291-7
Neuzil et al, JAIDS 2003;34:304-7

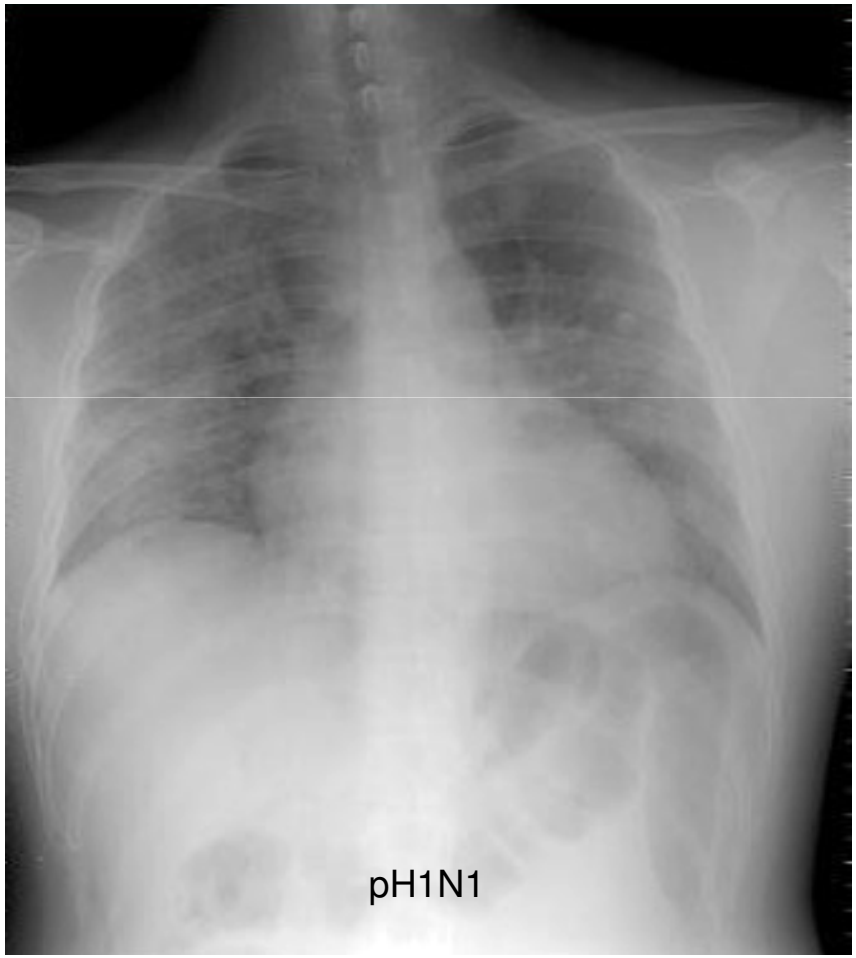
Fatal pandemic H1N1 in South African HIV-infected patients

Characteristics	
Tested	34
HIV-infected	18
Median CD4 count	58
On ART	4
Oseltamivir	9
Chest radiography	
– Bilateral infiltrates (10)	
– Multi-lobar consolidation	
– ARDS	

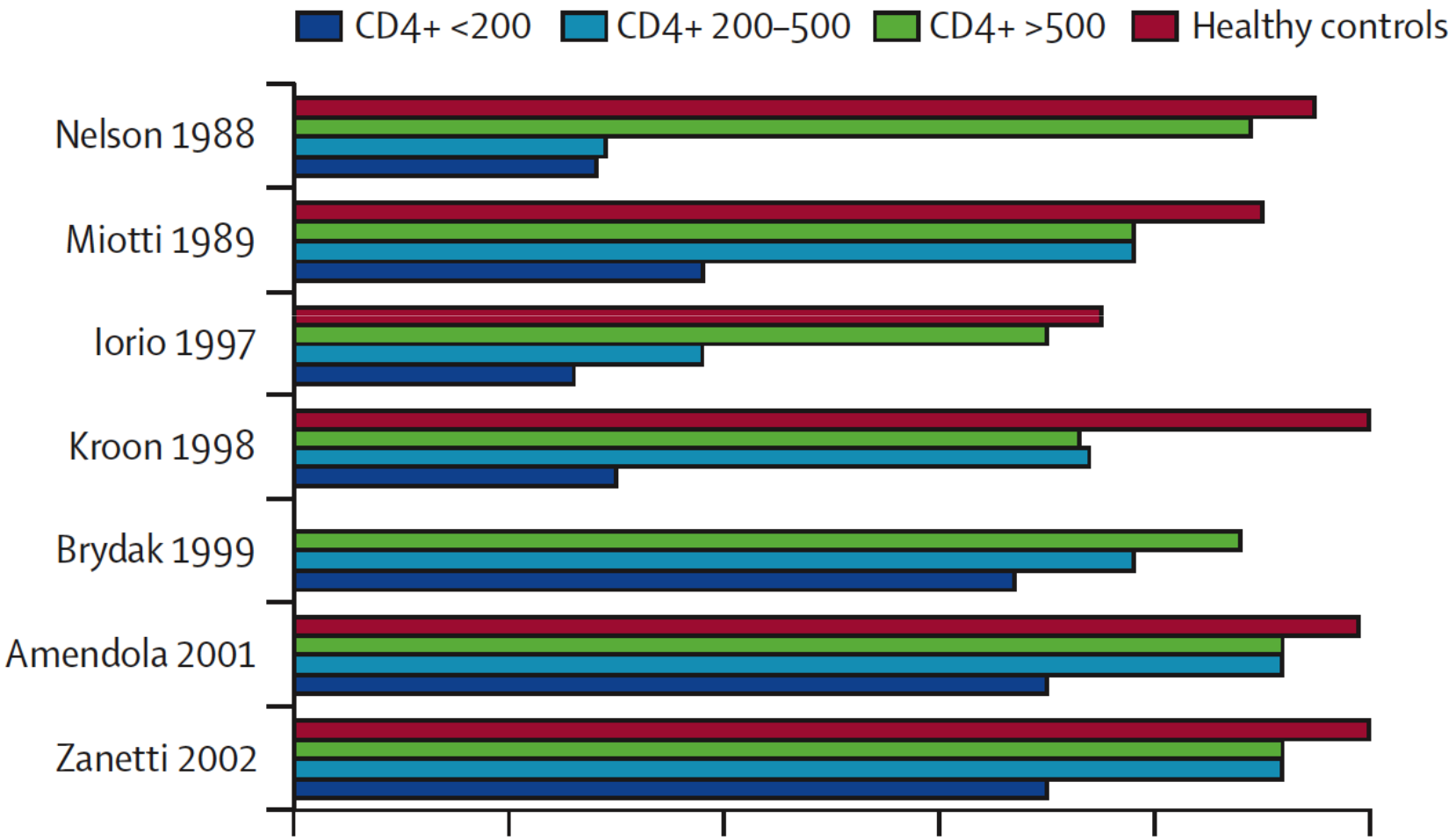
Co-morbidities	
Pregnant	10
COPD	4
Active TB	3
Cardiac	2
Diabetes	1
Obesity	1
S. pneumoniae	2

How much H1N1 did we miss?



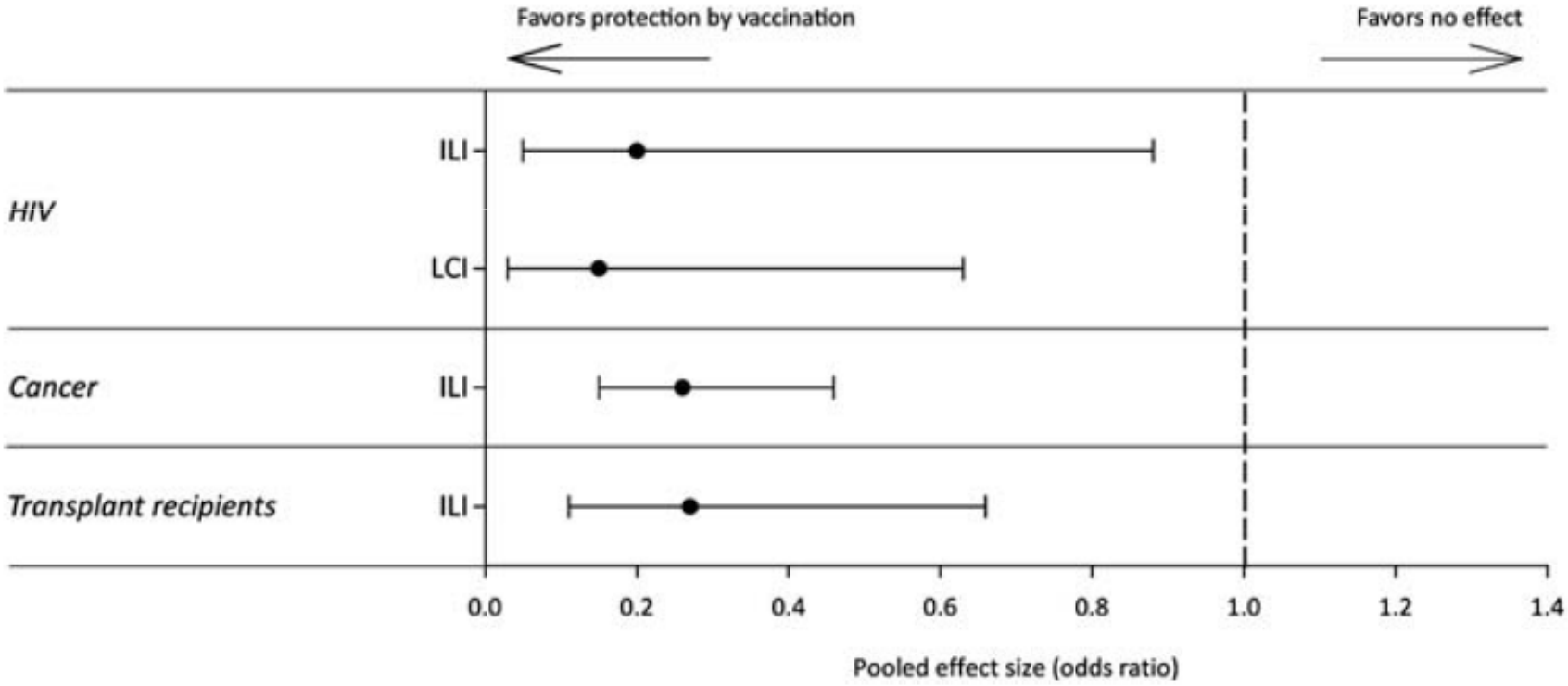


Protective post-vaccination influenza titres



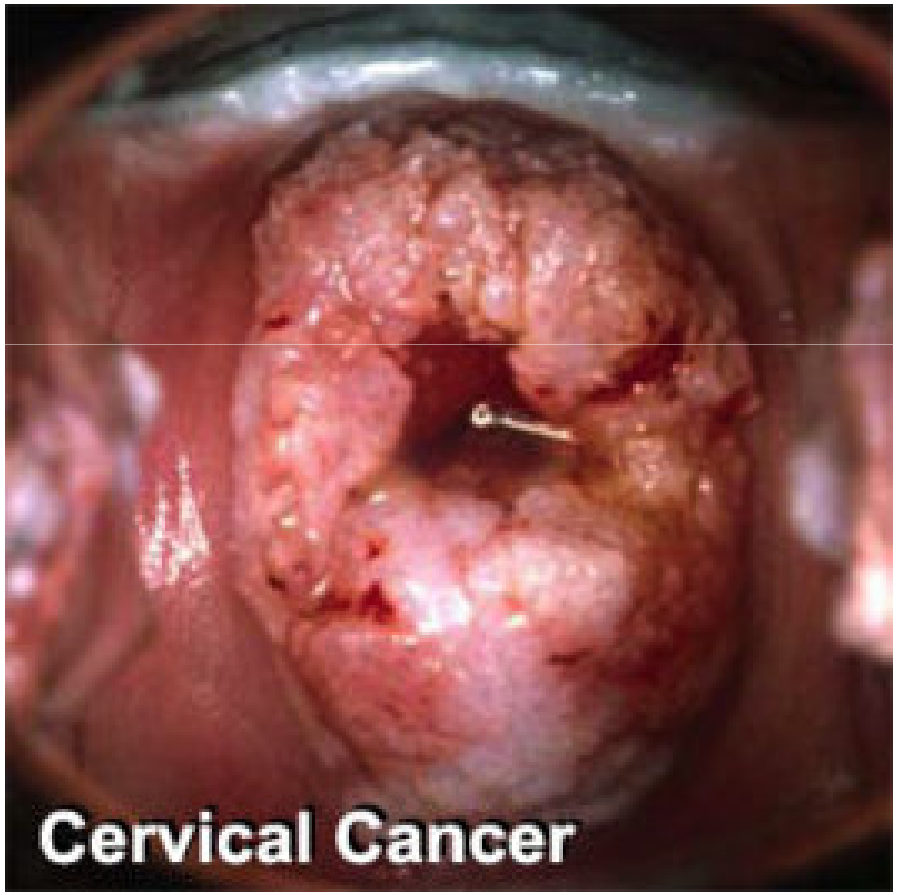
Kunisaki et al. Lancet Infect Dis 2009; 9: 493-504

Meta-analysis of influenza vaccine effect on ILI and lab-confirmed cases



Beck et al. J Infect Dis 2012;206:1250-9

Human Papillomavirus (HPV)



- HPV infection rates
  - 66% HIV-infected women
  - 90% MSM
- Higher risk of cervical and anal cancer
- Risk of anal cancer on ART remains 2-fold higher than HIV-uninfected patients

JID 1998;177(2):361-7. JAIDS 2009;51(3):274-82. 17th CROI 2010 Abstract 28

HPV Vaccines

	Gardasil	Cervarix
HPV strains covered	HPV-6, HPV-11 HPV-16, HPV-18	HPV-16, HPV-18
Prevention genital warts	98.8% in women 9-12yrs	Nil
Prevention CIN	98% cervical precancerous lesions from vaccine strains in HPV-uninfected vs 44% in all study participants	93% of CIN 2 or greater dypslasia in HPV-uninfected vs 30% overall population
Prevention of AIN in MSM 16-26yrs	95% persistent anal infections 75% high grade AIN from vaccine strains	Not studied
	NEJM 2007;356(19):1915-27 NEJM 2007;359(19):1928-43 NEJM 2011;364(5):401-11)	Lancet 2009;374:301-14

HPV vaccine efficacy in HIV

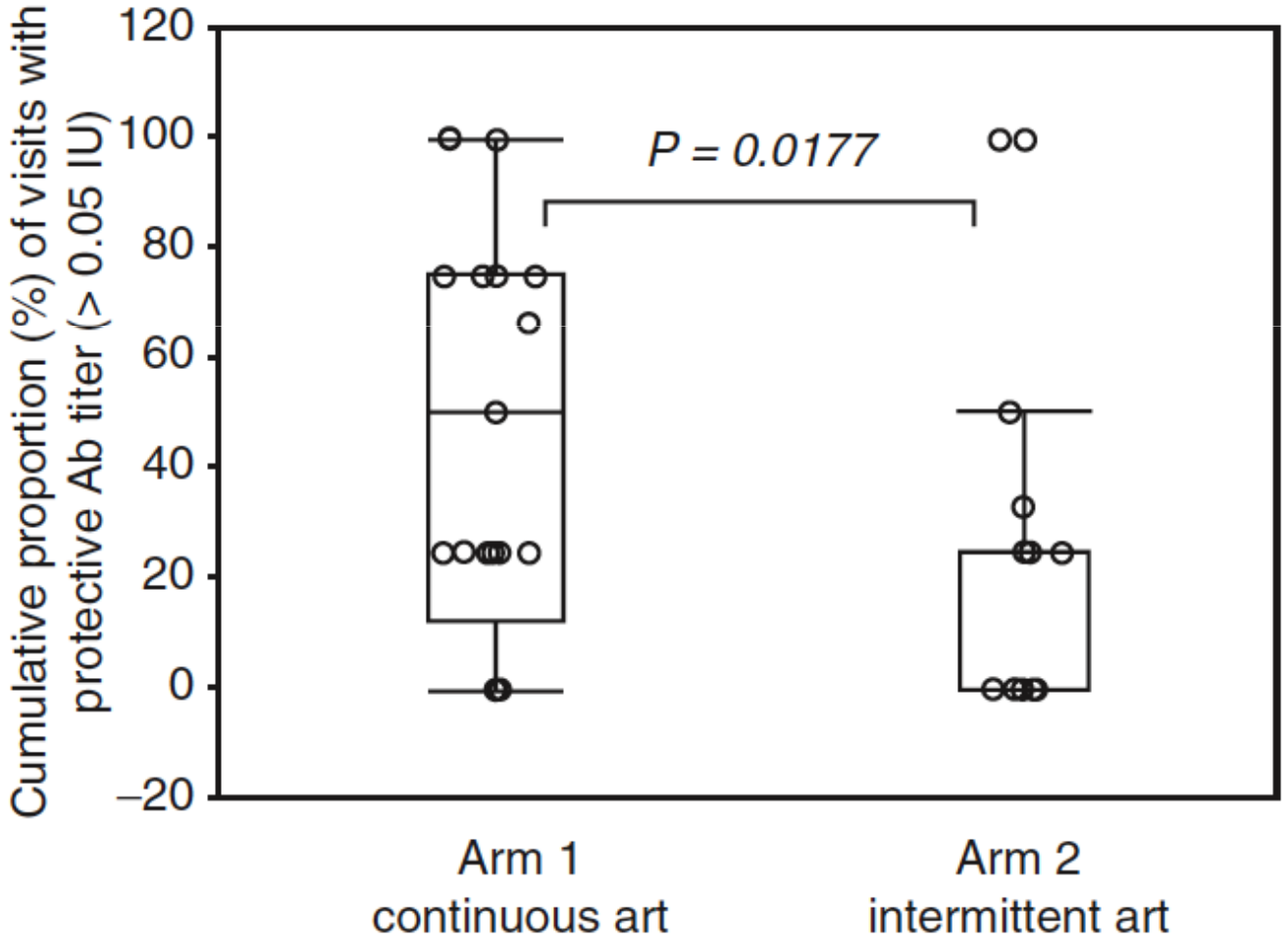
- Efficacy will depend on rates of HPV infection
  - HIV-infected women infected with HPV-16 (30%), HPV-18 (12-19%) and both (9%)
  - HIV-infected men – HPV-16 (50%) and HPV-18 (23%)
- Limited data of efficacy in HIV
  - Children with CD4% ≥15 – seroconversion rates >96% to all 4 strains
  - Men ≥18 yrs – without AIN had seroconversion rates >95%
  - Some evidence that seroconversion was less in MSM

18th CROI 2011. Abstracts 762, 763 and 871. JAIDS 2010;55(2):197-204

Principles of immunization in HIV-infected adults

- Vaccination is associated with HIV viral load blip and transient reduction in CD4 count
- Avoid live vaccines if CD4 count < 200 cells/mm^3
- Polysaccharide vaccines elicit poor antibody responses
- Extra booster doses are commonly employed but often without hard evidence
- Either delay vaccination until ART reconstitutes immunity or repeat once CD4 count >200 cells/mm^3

Interrupted ART decreases protective antibody titres to neoantigens



Azzoni et al. AIDS 2012;26:1355-62

Summary

- Quantitative and qualitative defects in innate and adaptive immunity limit vaccine responses in HIV
- In patients with CD4 counts <200 cells/mm^3 avoid live vaccines and if possible reconstitute the immune system prior to vaccination or revaccinate once reconstitution has occured
- Do not miss the opportunity to limit vaccine-preventable infections in your patients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