NATIONAL HEALTH LABORATORY SERVICE

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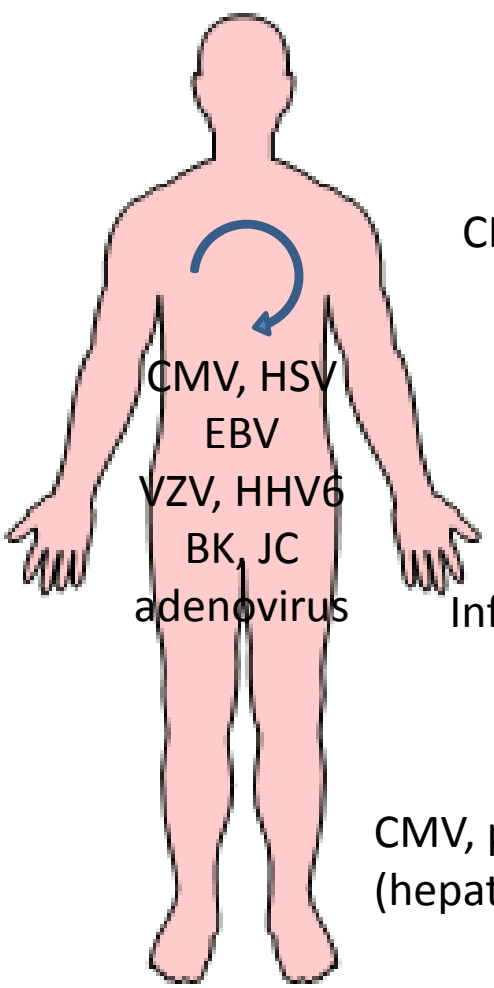
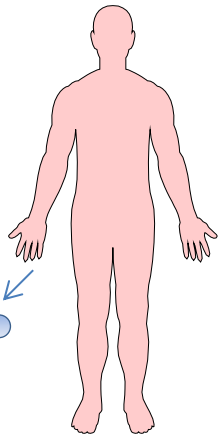
Prophylaxis and treatment of viral infections in HSCT

Diana Hardie

viral infection in HSCT recipients can come from various sources:

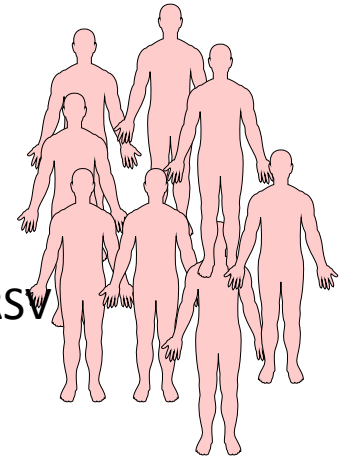


Recipient



Donor (antiviral T cells)

CMV, EBV



Community acquired:
Hospital staff,
household contacts

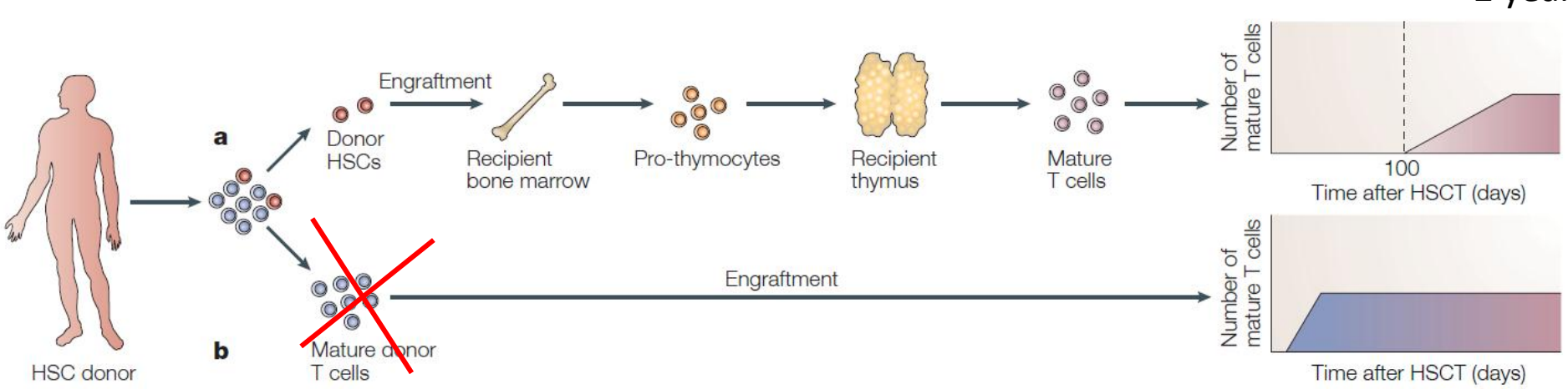
Respiratory viruses,
Influenza, adenovirus, RSV
Enteric viruses,
other

CMV, parvovirus
(hepatitis)

Blood products

Factors associated with increased risk of viral infection:

Antiviral immunity relies on functional T cells



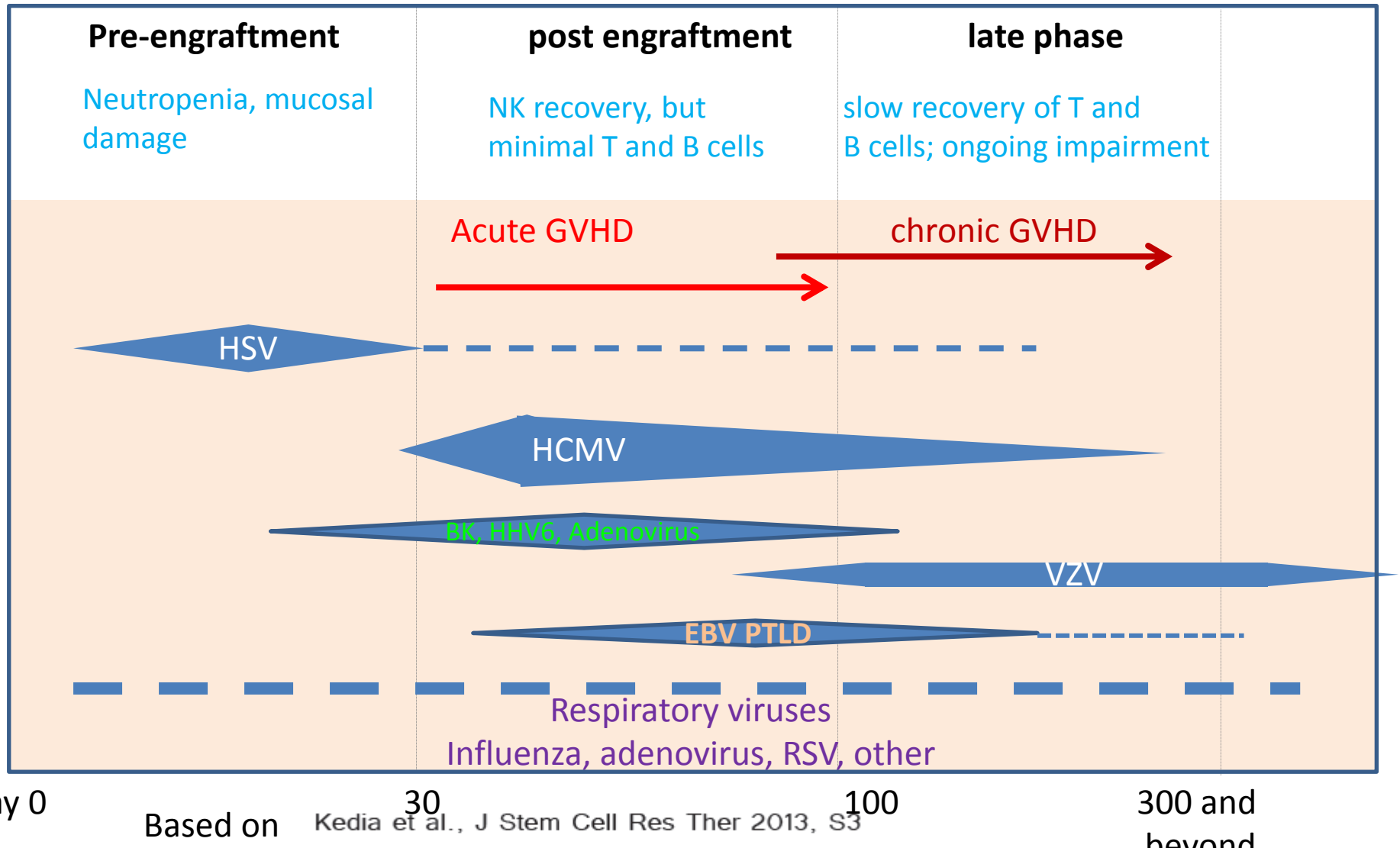
Nature Reviews immunology January 2005

Increased risk relates to
Poor and late reconstitution:

- T cell depletion of graft
- Allogeneic grafts
- -unrelated
- -HLA mismatch
- Cord blood grafts
- Repeat transplant
- GVHD (immune attack on TEC)
- Older age

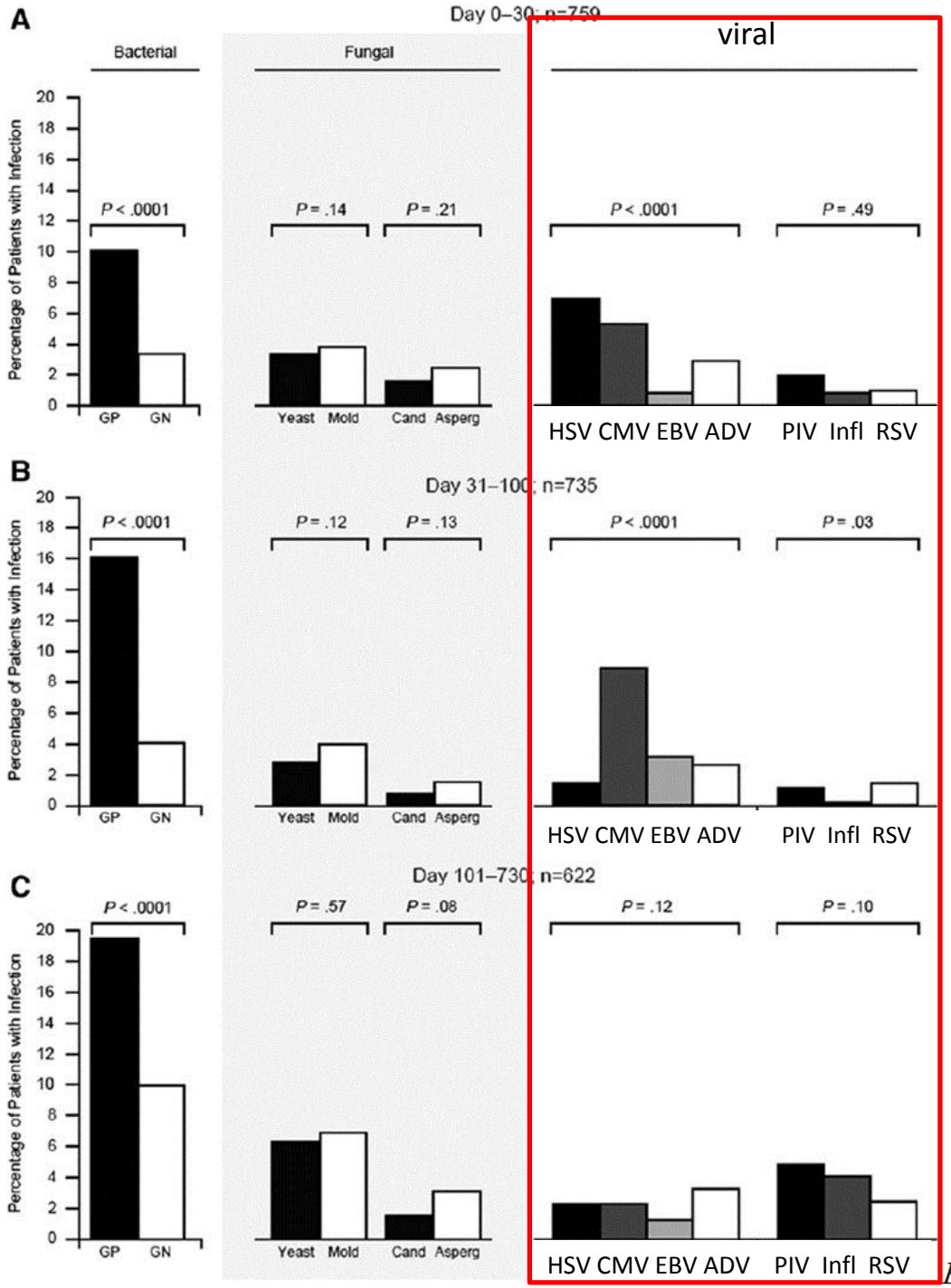
Time course for viral infections

Different viruses cause trouble at predictable times post transplant.



Based on Kedia et al., J Stem Cell Res Ther 2013, S3

Infectious disease burden



Day 0-30

n=739
Child, adolescents
48% T cell depleted

Day 31-100

Day 101-730

Biol Blood Marrow Transplant. 2013 January ; 19(1): 94–101

Human cytomegalovirus

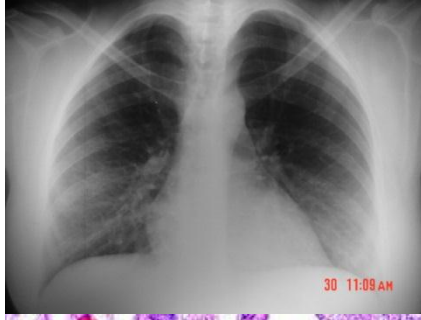
Number 1
R+/D-

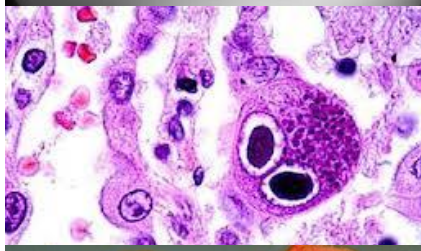
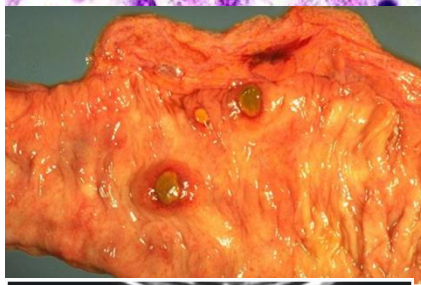
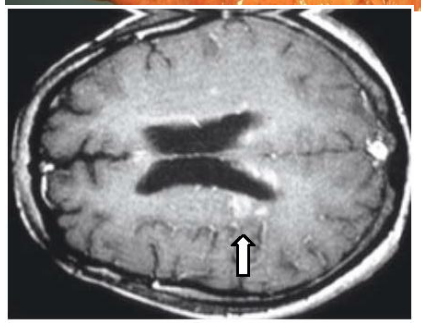
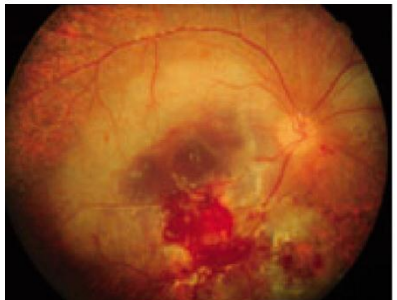
Disease burden reduced with
-Improved early detection of viraemia
-Pre-emptive therapy

Pre-emptive therapy preferred to prophylaxis

Traditionally, pp65 antigen in WBCs
RealTime qPCR

Thresholds to trigger pre-emptive therapy:
- any positive >200 genome copies/ml
- positive on 2 consecutive occasions
- viral load above log 3

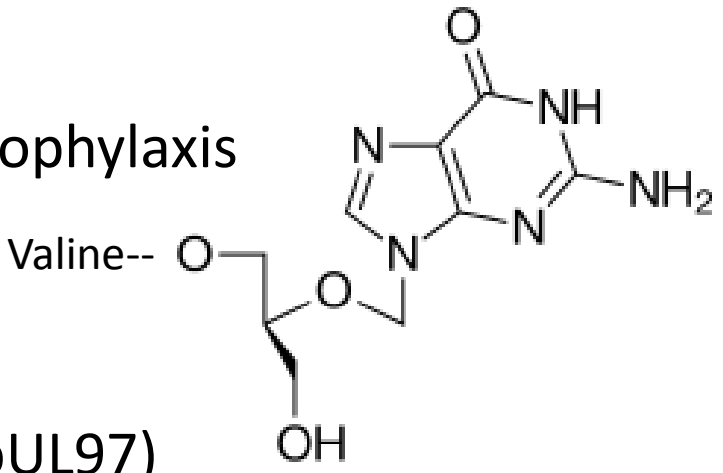


Ganciclovir/valganciclovir:

Drug of choice for treatment and prophylaxis

Acyclic anologues of guanosine



Mono-phosphorylated by viral TK (pUL97)
myelotoxicity

Drug resistance: pUL97 or pUL54

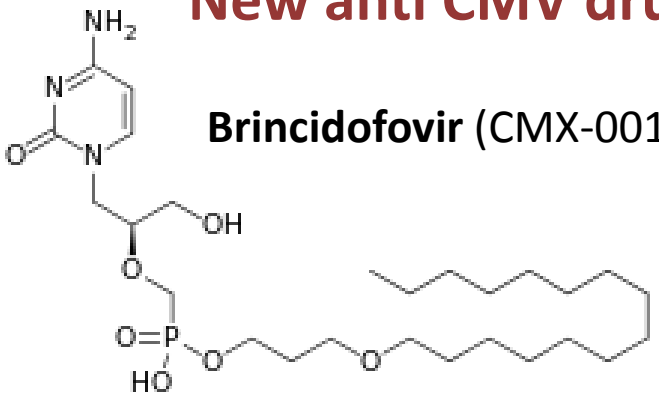
2nd and 3rd line agents:

Foscarnet and **cidofovir:**

Modest anti CMV activity and significant toxicity

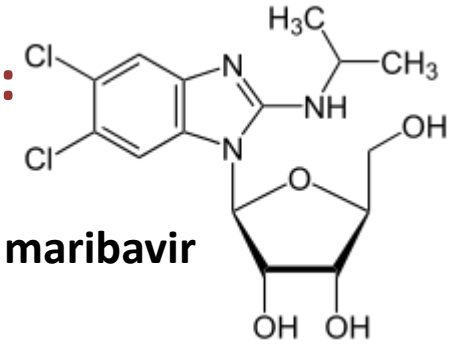
New drugs…

New anti CMV drugs in the pipeline:



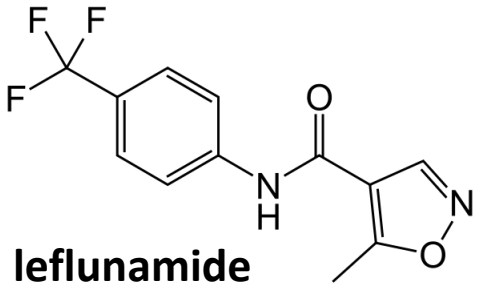
Brincidofovir (CMX-001)

Lipid conjugate of CDV
Acyclic nucleotide inhibitor of UL54
Lower toxicity, long t1/2
Broad spectrum activity against DNA viruses:
CMV, adenovirus, polyomaviruses, pox viruses
Phase 2 CMV prophylaxis trial(260 HSCT):
Significantly better than placebo
Dose limiting diarrhoea



maribavir

Targets pUL97
Low toxicity, effective in phase 2 trials
No benefit in phase 3 prophylaxis trial
- Dose too low
- Low rate of CMV events
Resistance pUL97 and pUL27



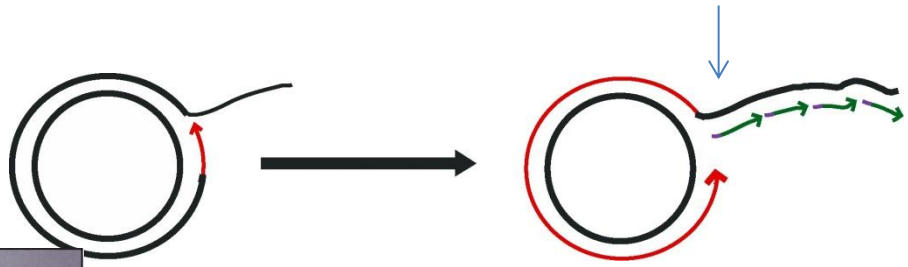
leflunamide

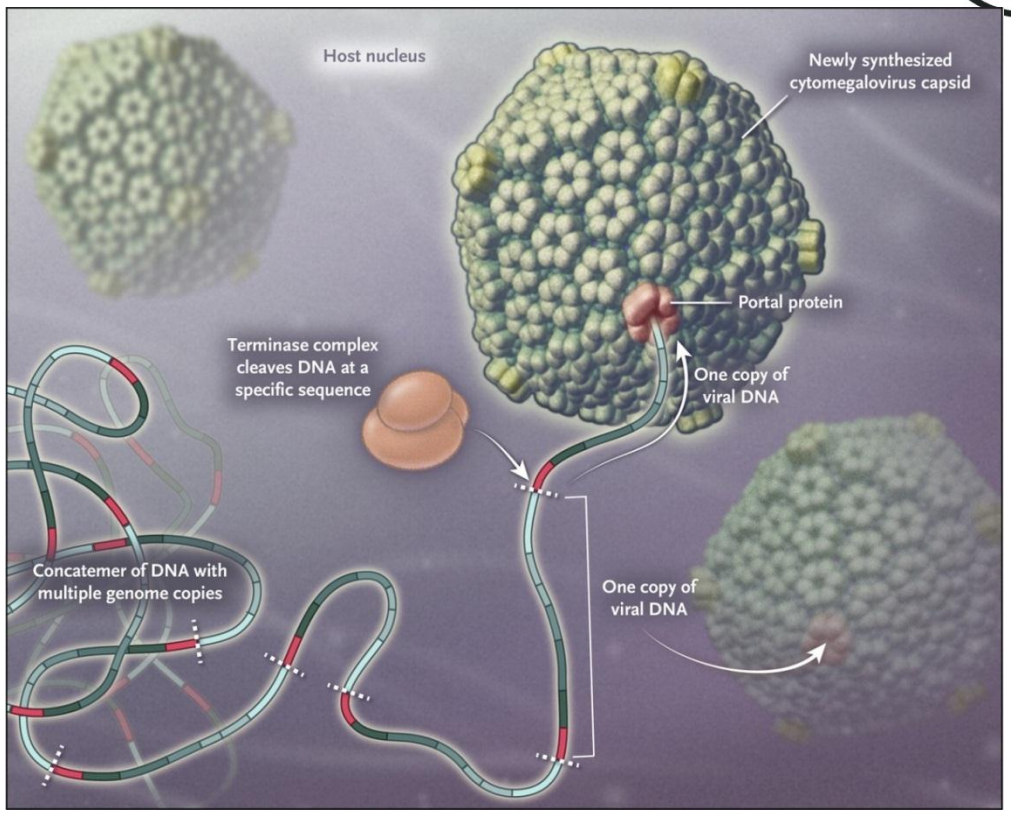
Immunosuppressive agent
Activity against CMV, HSV, BK
Blocks virion assembly

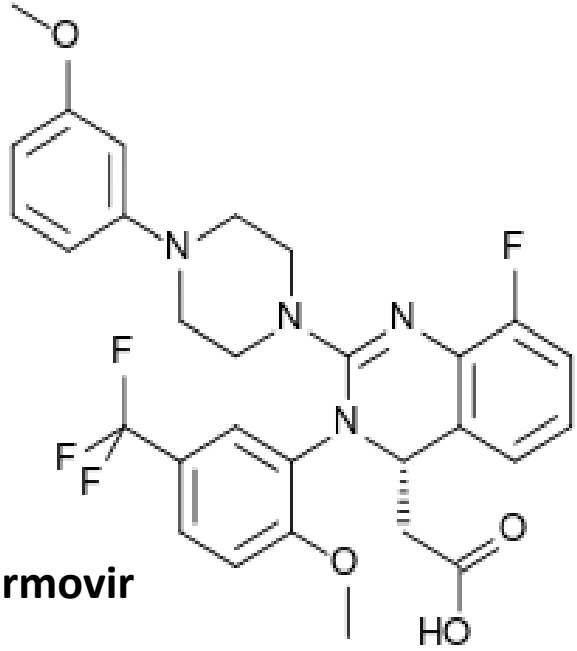
Letermovir

Targets the viral terminase:

Cleaves viral genomes







letermovir

Griffiths PD, Emery VC. N Engl J Med 2014;370:1844-1846.

Resistance conferred by a single point mutation in UL56 (terminase)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 8, 2014 VOL. 370 NO. 19

Letermovir for Cytomegalovirus Prophylaxis in Hematopoietic-Cell Transplantation

Roy F. Chemaly, M.D., Andrew J. Ullmann, M.D., Susanne Stoelben, M.D., Marie Paule Richard, M.D., Martin Bornhäuser, M.D., Christoph Groth, M.D., Hermann Einsele, M.D., Margarida Silverman, M.D., Kathleen M. Mullane, M.D., Janice Brown, M.D., Horst Nowak, Ph.D., Katrin Kölling, M.Sc., Hans P. Stobernack, D.V.M., Peter Lischka, Ph.D., Holger Zimmermann, Ph.D., Helga Rübsamen-Schaeff, Ph.D., Richard E. Champlin, M.D., and Gerhard Ehninger, M.D., for the AIC246 Study Team*

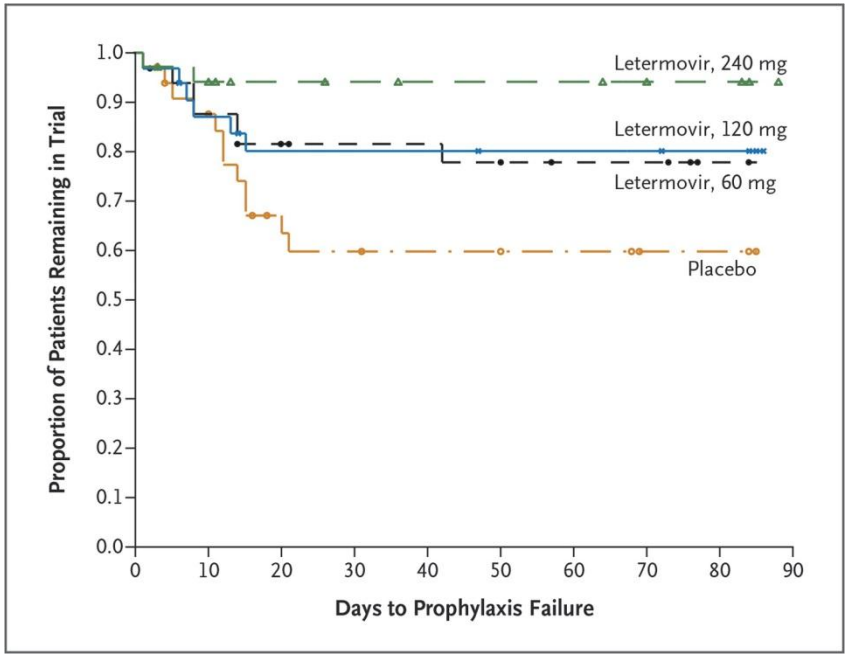
Phase 2 prophylaxis trial:
131 CMV sero-positive allo-HSCT recipients

Incidence and time to failure of prophylaxis
3 dosages, 12 weeks
60, 120, 240 mg or placebo

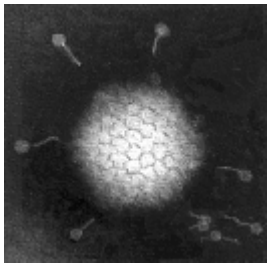
Dose dependent reduction in CMV viraemia episodes
Safety profile similar to placebo

Phase 3 trial is planned…

KM plot of time to failure of prophylaxis:



Adenoviral disease

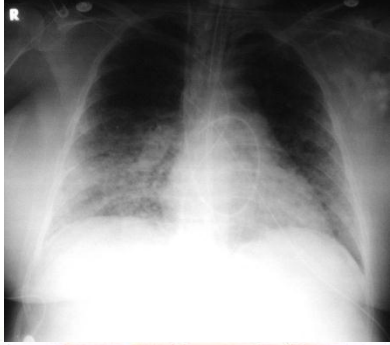


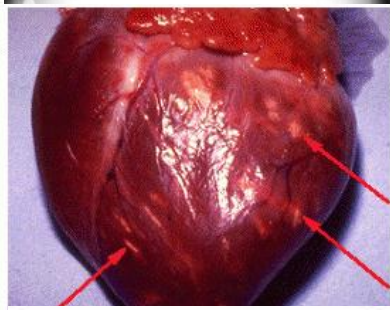
Un-enveloped dsDNA virus
57 Human Adv types, 7 species
Range of clinical disorders
RTI, gastro-enteritis, kerato-conjunctivitis
Highly resistant to inactivation
Nosocomial outbreaks

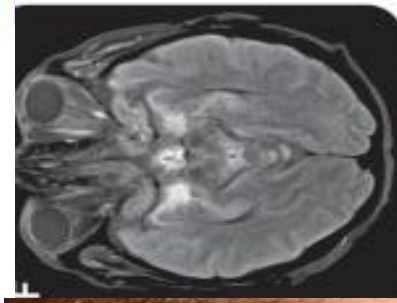
HSCT:

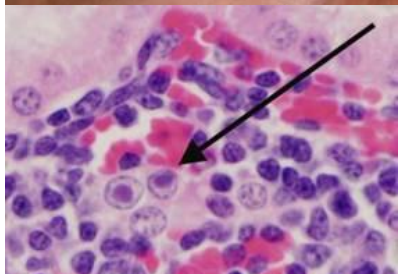
Horizontal acquisition or reactivation

Children>> adults
First 100 days
Disseminated infection:
-preceded by viraemia
Pneumonia, enteritis, myocarditis, encephalitis

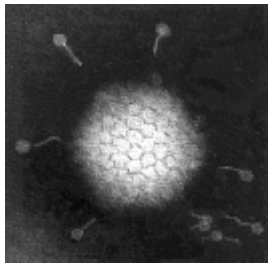








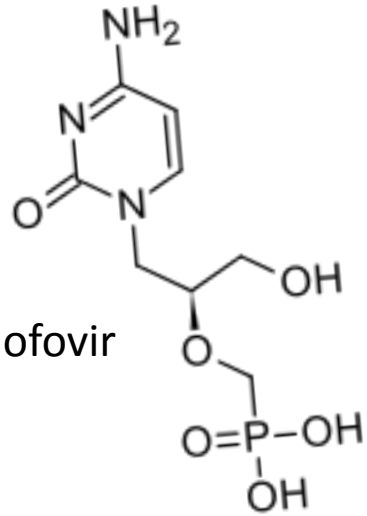
European Conference for Infections in Leukaemia: Recommendations in Allogeneic HSCT:



Transplant Infectious Disease 2012: **14**: 555–563

Diagnostics:

Blood monitoring advised in at risk patients
qPCR based methodologies preferred
>4log10 copies/ml or rapidly rising VL



cidofovir

Prophylaxis and therapy of adenoviral infections:

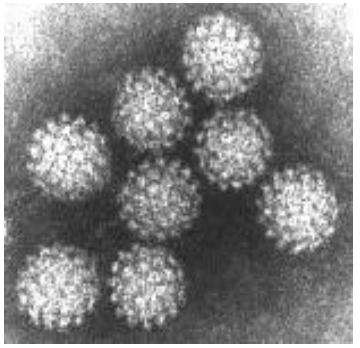
Prophylaxis is not recommended
Pre-emptive therapy when viraemia is detected (high risk only)

In suspected disease:

Reduce immuno-suppression if possible,
IV cidofovir
Ribivirin not recommended
donor derived HAdV-specific T cells –only in experienced centre

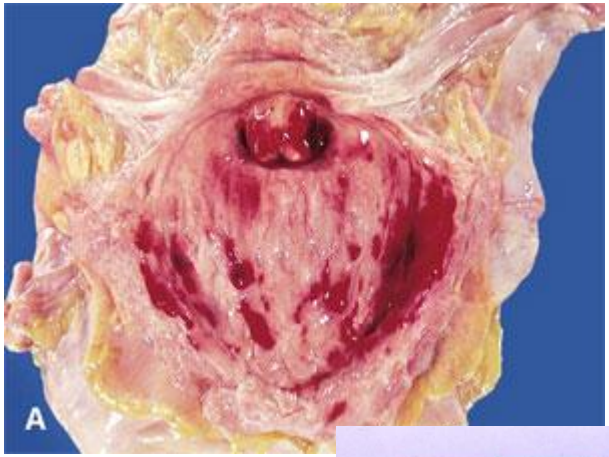
Brincidofovir?? Only case reports so far

BK polyomavirus



BK virus and its role in Haematopoietic stem cell transplantation: evolution of a pathogen
Curr Infect Dis Rep (2014) 16; 417

Ubiquitous infection
Primary infection ⟶ persistent
Renal tract
Shed in urine in 50-80% HSCT



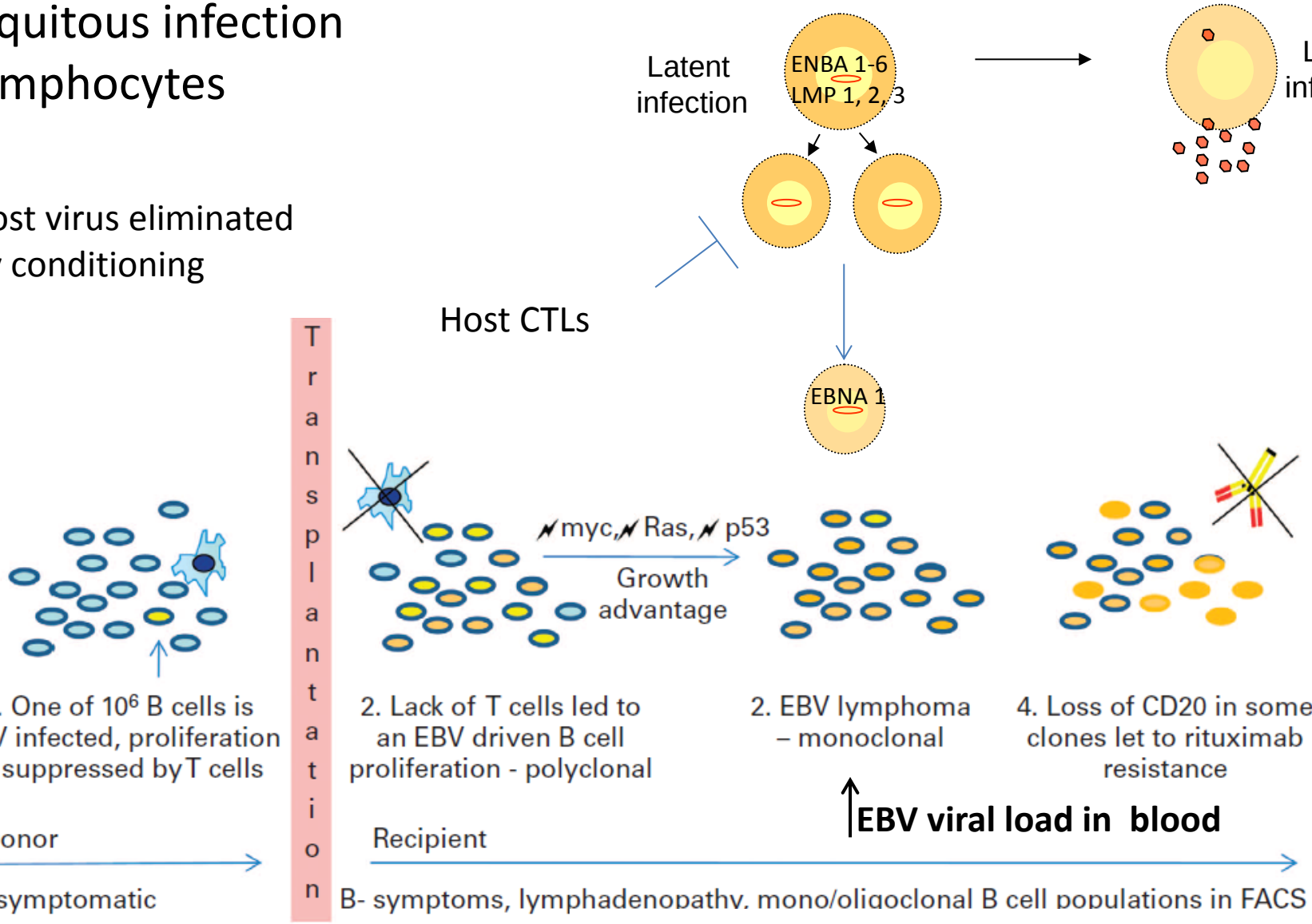
Clinical associations:
Haemorrhagic cystitis (late)
Encephalitis, pneumonitis, vasculopathy, retinitis
Poorer outcome

Diagnosis:
High viral load in blood and urine with compatible clinical disease

Therapy:
Reduced immunosuppression
Cidofovir, Leflunomide no RCTs, toxicity

EBV and Post Transplant Lympho-proliferative Disorder

Ubiquitous infection
B lymphocytes

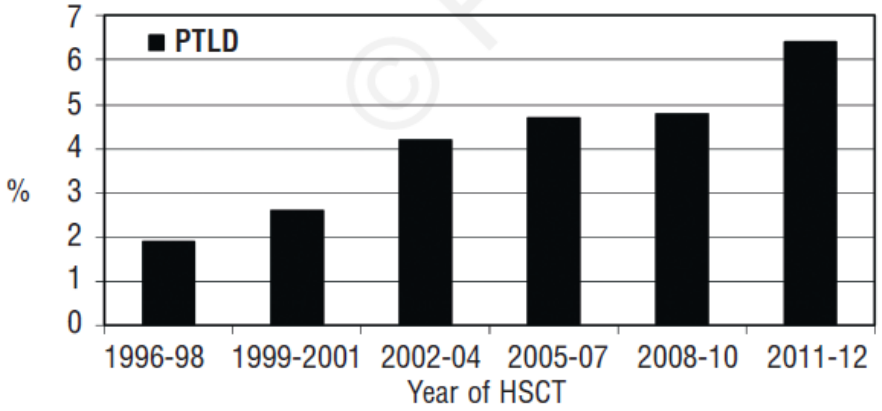


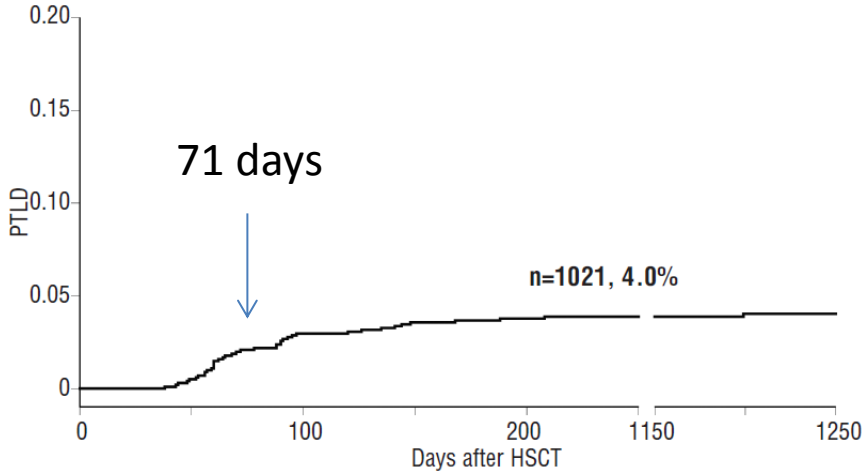
Bone Marrow Transplantation (2013), 1–5

Risk Factors for EBV associated PTLD after allogeneic HSCT

Haematologica (2014) 99 (2), p346-352

Retrospective analysis of PTLD cases in 1021 HSCT patients between 1996-2011
Karolinska Institute





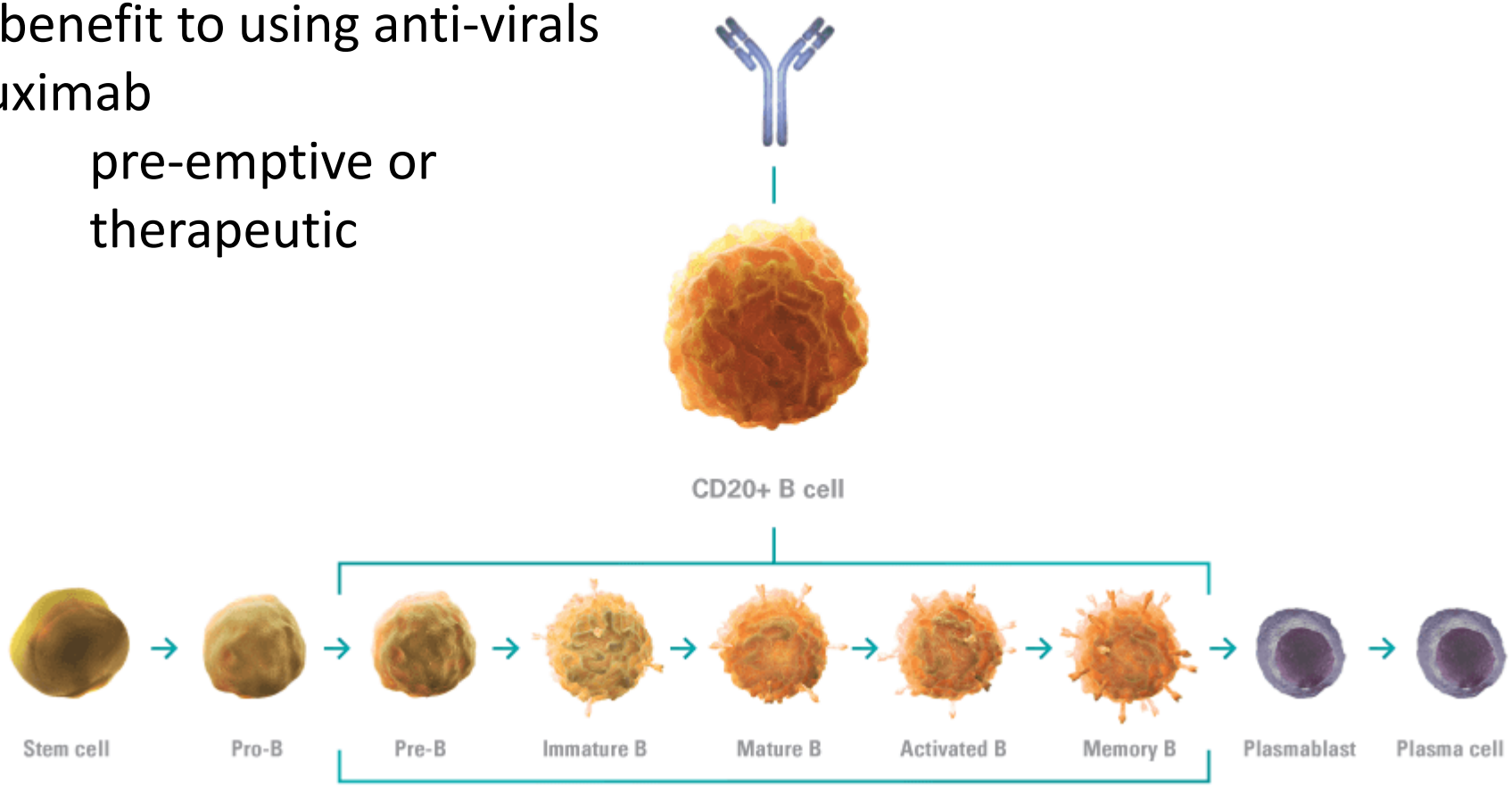
Risk factors:

T cell depletion
Recipient age >50
Second allogeneic graft
GVHD
Cord blood graft

Poor and late T cell reconstitution

Principles of therapy:

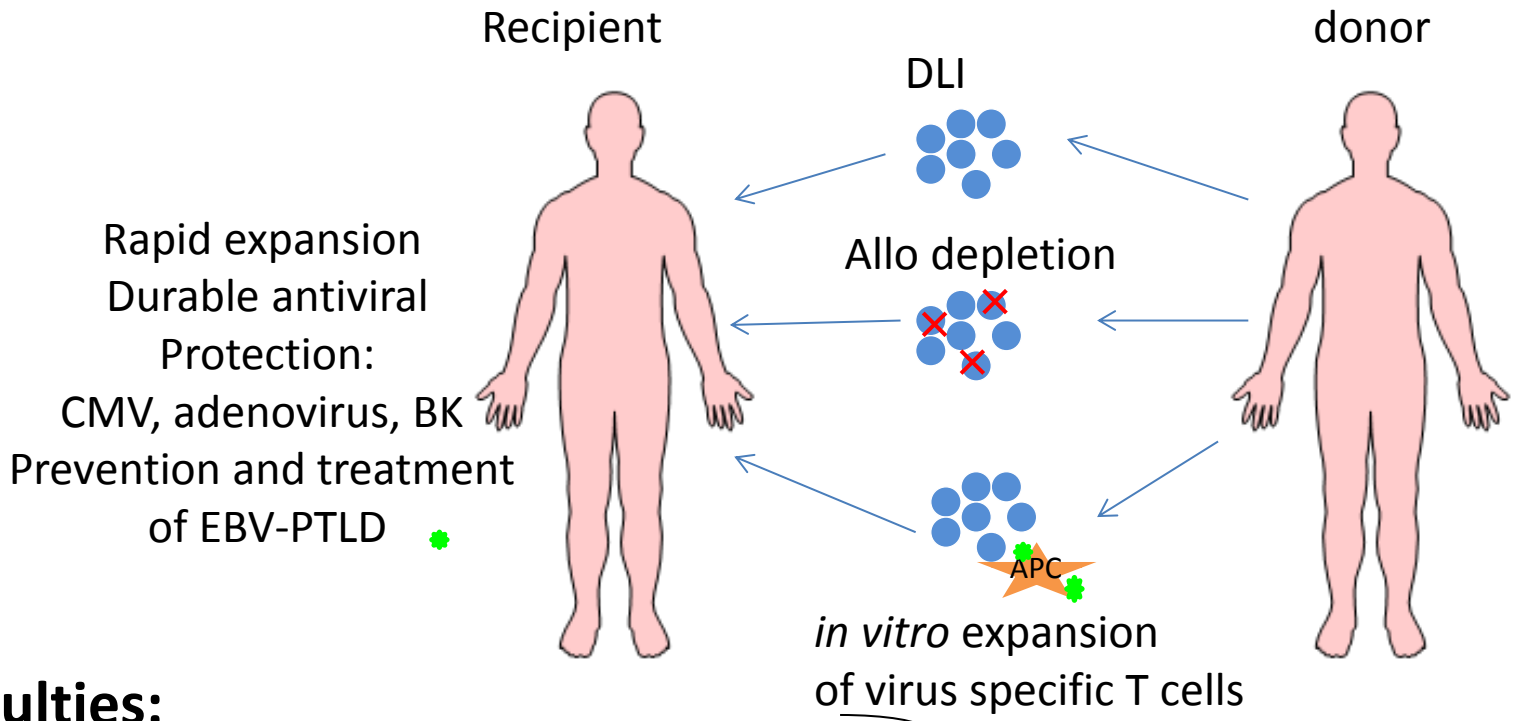
Reduction in immunosuppression
No benefit to using anti-virals
Rituximab
pre-emptive or
therapeutic



Adoptive immunotherapy - an alternative approach…

Adoptive transfer of donor derived virus specific T cells

Highly effective at controlling infection in multiple phase 1 trials



Difficulties:

time delay before cells are ready for use
Complex manipulations *ex vivo*,
Technologies for expanding virus specific CTLs
Potential allo-reactivity (GVHD)
Sero-negative donors, cord blood grafts

Limits widespread use

Table 1 Clinical trials using *in vitro* expanded VSTs

Stimulation	*Target*	*Patients*	*Prophylaxis or treatment (number of patients)*	*Viral outcomes*	*References*
CMV-infected fibroblasts	CMV	14	Prophylaxis	No CMV infections	Walter *et al.*[62]
CMV lysate-stimulated PBMCs	CMV	8	Treatment	6 CR 1 PR 1 NR	Einsele *et al.*[63]
CMV antigen-pulsed DCs	CMV	28	Prophylaxis Treatment	23 Responded to VSTs with antivirals	Peggs *et al.*[66]
pp65-pulsed or Ad5f35pp65 vector-transduced DCs	CMV	50	Prophylaxis	26 Patients developed CMV infections 9 Required antivirals 1 CMV-related death	Blyth *et al.*[69]
EBV-LCLs	EBV	118	Prophylaxis (105) Treatment (13)	No new EBV infections 11 CR 2 Deaths	Rooney *et al.*[70] Heslop *et al.*[71] Rooney *et al.*[72] Heslop *et al.*[20]
EBV-LCLs	EBV	6	Treatment	5 Displayed a decrease in viral load 1 EBV-related death	Gustafsson *et al.*[74]
EBV-LCLs	EBV	3	Treatment	3 CR	Comoli *et al.*[73]
EBV-LCLs	EBV	19	Treatment	13 CR 1 EBV-related death	Dubrovina *et al.*[75]
Ad5f35pp65 vector-transduced EBV-LCLs and PBMCs	EBV AdV CMV	11	Prophylaxis (10) AdV treatment (1)	3/3 CR of EBV infection/PTLD 3/3 CR of CMV infection 6/6 CR of AdV infection/disease	Leen *et al.*[77]
Plasmid-nucleofected DCs	EBV AdV CMV	10	EBV treatment (4) AdV treatment (5) CMV treatment (5)	3 CR 5 CR 4 CR, 1 patient with persistent colitis proceeded with colectomy	Gerdemann *et al.*[82]

Abbreviations: AdV, adenovirus; CMV, cytomegalovirus; CR, complete response; DC, dendritic cell; EBV, Epstein–Barr virus; EBV-LCL, EBV-transformed B lymphoblastoid cell line; NR, non-responder; PBMC, peripheral blood mononuclear cell; PR, partial response; PTLD, post-transplant lymphoproliferative disease; VST, virus-specific T cell.

3rd party T cells?

Banked HLA matched antiviral T cells from miscellaneous donors
Only phase 1 trials so far
Safe, immediate
Efficacy depends on HLA match

Cytotherapy, 2014; 16: 149–159

ith the use of third-party CTL for viral infections after stem cell transplant.

n	Target	Type of HSCT	Serious Adverse Events	Results
5	EBV	Cord blood	None	➢ 4 patients achieved CR ➢ 1 patient had disease progressi
1	EBV	Cord blood	None	➢ CR ➢ Subsequent relapse treated with 2nd CTL infusion
44	EBV, CMV, AdV	MRD, MUD, cord blood	➢ 8 cases of GvHD after CTL (2 cases of *de novo* GvHD and 6 cases of GvHD recurrence)	➢ 82% CR and partial remission
1	Adv	MMUD	Grade II-IV GvHD (skin, liver)	➢ AdV clearance ➢ Patient died of CMV

Post transplant vaccination:

Re-vaccination is recommended 2 years post HSCT
Responses depend on degree of T cell recovery

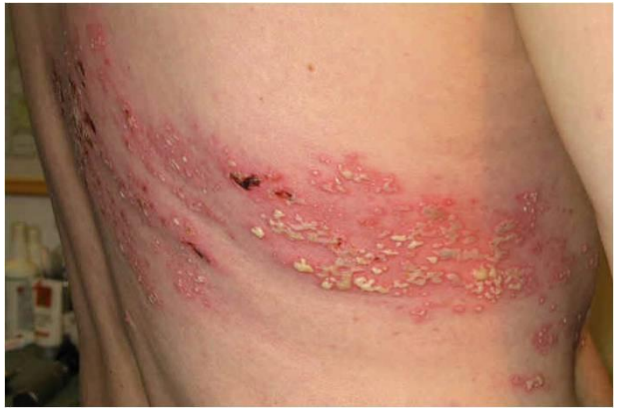
Best in children

virus	timing	frequency
Influenza	4-6 months	annually (patient and contacts)
Inactivated polio	6-12 months	3 doses
Hepatitis B	6-12 months	3 doses
Measles*	>24 months	1-2 doses
Mumps *		
Rubella*		

Biol Blood Marrow Transplant 15:1143-1238, 2009

* Only if off immuno-suppression, no GVHD

Zoster vaccine?



Biol Blood Marrow Transplant 20: 285-7, 2014

Safety in 110 HSCT patients
Single dose, 2 years post transplant
2 patients developed zoster rash within 42 days of vaccine
None in 1178 months follow up