Hematopoietic Stem Cell Transplant (HCT) in HIV+ Patients: Clinical Pearls

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Disclosures

- I have no conflicts of interest to declare.

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Objectives

- Summarize the treatment of HIV-associated lymphoma in the post combination antiretroviral therapy (cART) era.
- Summarize the use of autologous stem cell transplantation (AutoSCT) for the management of HIV-associated lymphoma.
- Examine the current literature on using allogeneic stem cell transplantation (AlloSCT) for the management of hematologic malignancies in HIV-infected patients.
- Recognize the pharmaceutical considerations and potential drug-drug interactions for HIV-infected patients receiving hematopoietic stem cell transplant (HCT).

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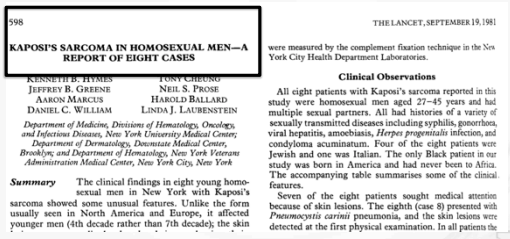
HIV & Cancer



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KAPOSI'S SARCOMA IN HOMOSEXUAL MEN—A REPORT OF EIGHT CASES

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Summary The clinical findings in eight young homosexual men in New York with Kaposi's sarcoma showed some unusual features. Unlike the form usually seen in North America and Europe, it affected younger men (4th decade rather than 7th decade); the skin

were measured by the complement fixation technique in the New York City Health Department Laboratories.

Clinical Observations

All eight patients with Kaposi's sarcoma reported in this study were homosexual men aged 27–45 years and had multiple sexual partners. All had histories of a variety of sexually transmitted diseases including syphilis, gonorrhoea, viral hepatitis, amoebiasis, *Herpes progenitalis* infection, and condyloma acuminatum. Four of the eight patients were Jewish and one was Italian. The only Black patient in our study was born in America and had never been to Africa. The accompanying table summarises some of the clinical features.

Seven of the eight patients sought medical attention because of skin lesions. The eighth (case 8) presented with *Pneumocystis carinii* pneumonia, and the skin lesions were detected at the first physical examination. In all patients the

Hymes, KB et al. Lancet 1981, 2(8247):598-600

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The rise of AIDS/HIV-related lymphomas

- 1981-Primary central nervous system non-Hodgkin lymphoma (NHL)
- 1985 – systemic NHL recognised as an AIDS defining cancer
- 1996 – Primary effusion lymphoma (PEL)
- 1997 - Plasmablastic NHL

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The rise of non AIDS-defining Cancers

- HIV infected individuals are at an increased risk of developing other haematological cancers:
  - Hodgkin lymphoma (11-14 fold)
  - Leukemia (3 fold)
  - Multiple Myeloma (3 fold)
- These cancers are <u>not</u> classified as AIDS-defining cancers. Non-AIDS defining Cancer (NADC).

Spano JP et al. Eur J Intern Med 2002;13(3):170-9
Grulich, A et al. Lancet 2007;370(9581):59-67

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Heightened risk of non-AIDS defining Cancers in people with HIV

- Incidence of cancer is higher in people with HIV, and it is not just the AIDS-defining cancers but also the non-AIDS-defining cancers.
- Immunosuppression has a strong link to cancer.
- CD4+ cell count does not always have a linear relationship with the risk of cancer.

Grulich, A et al. Lancet 2007;370(9581):59-67

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Baseline characteristics for 16 patients with HIV-associated Hodgkin Lymphoma

	PI-based cART n(%)	Non-PI based cART n(%)	Total n(%)	*P*- value
Number (n)	10	6	16	
Median [range] age at HL diagnosis in years	49 [40-59]	42.5 [34-59]	44 [34-59]	**0.35§**
Male gender	10	6	16	
HIV Risk (MSM)	10	6	16	
Prior AIDS	5 (50)	0 (0)	5 (31)	**0.05***
Median [range] CD4 cell count at HL diagnosis (cells/uL)	190.5 [14-768]	296 [117-970]	233.5 [14-970]	**0.43§**
HIV Viral load at HL diagnosis				
≤50 copies/mL	6 (60)	5 (83)	11 (69)	**0.59***
>50 copies/mL	4 (40)	1 (17)	5 (31)	
Hepatitis B co-infection (Known positive)	2 (20)	2 (23)	4 (25)	**0.6***
Hodgkin lymphoma stage				
I-II	4 (40)	3 (50)	7 (44)	**1***
III-IV	6 (60)	3 (50)	9 (56)	
Hasenclever IPS risk				
Good risk (0-1)	3 (30)	3 (50)	6 (37)	**0.8***
Fair risk (2-3)	2 (20)	1 (17)	3 (19)	
Poor risk (4-7)	5 (50)	2 (23)	7 (44)	
B-symptoms	7 (70)	5 (83)	12 (75)	**1***
Elevated LDH	4 (40)	3 (50)	7 (44)	**1***
Bone Marrow involvement	3 (30)	3 (50)	6 (37.5)	**0.6***
Extranodal involvement	5 (50)	3 (50)	8 (50)	**1***

*P-value using Fisher's exact test §P-value using Mann-Whitney U test
IPS= International Prognostic Score for Hodgkin lymphoma LDH= Lactate dehydrogenase

Ibrahim K and Milliken S. (Abstract 744). 20th Conference on Retroviruses and Opportunistic Infections (CROI), March 3-6, 2013, Atlanta, USA

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Treatment of HIV-related lymphomas

- In the pre-cART era (before 1996)
  - Poor outcomes using different chemotherapy regimens.
  - Short overall survival (OS) time of 5-8 months.
  - High rate of opportunistic infections.
  - High relapse rate.

cART= combination antiretroviral therapy

Levine et al. Cancer 1991;68(11):2466-72.
Fisher et al. NEJM 1993;328(14):1002-6
Kaplan et al. NEJM 1997;336(23):1641-8.

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Treatment of HIV-related lymphomas

In the post-cART era- the picture has changed!

- Patients are better able to tolerate standard & intense chemotherapy regimens.
- Much improved outcomes with chemotherapy.
- Survival outcomes-similar to those seen with non-HIV patients with lymphoma.

Ribera JM, et al. BMJ 2008;140(4):411-9.
Sparano JA, et al. Blood 2010;115(15):3008-16.

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Rituximab + chemotherapy for HIV-NHL

Study	Rx	Sample size	Complete Response	Overall survival
*Kaplan et al. Blood 2005 [1]	R-CHOP vs. CHOP	149	57% vs. 47%	55% @ 2-year
Boue et al. JCO 2006 [2]	R-CHOP	61	67%	75% @ 2-year
Spina et al. Blood 2005 [3]	R-CDE	74	70%	64% @ 2-year
Ribera et al. BMJ 2008[4]	R-CHOP	81	69%	56% @ 3-year
Sparano et al Blood 2010 [5]	R-EPOCH vs. EPOCH then R	106	73% vs. 55%	70% vs. 67% @ 2-year

*Infection-related deaths occurred more in the R-CHOP arm (14% vs. 2%) *p*=0.035

R-CHOP = Rituximab-cyclophosphamide, doxorubicin, vincristine and prednisolone
CDE= cyclophosphamide, doxorubicin, etoposide
EPOCH= etoposide, prednisolone, vincristine, cyclophsphamide, doxorubicin

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ABVD for HIV-associated Hodgkin Lymphoma

- 224 patients with Hodgkin lymphoma treated with ABVD
- (93 HIV+ve, 131 HIV-ve)- *94% of HIV patients were on cART*

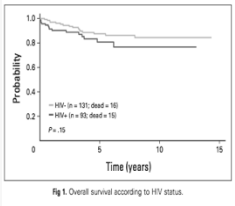

Fig 1. Overall survival according to HIV status.

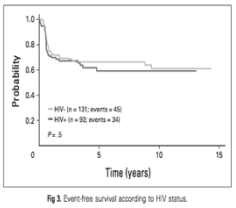

Fig 3. Event-free survival according to HIV status.

ABVD= Adriamycin/Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine

Montoto et al. JCO 2012; 30(33):4111-6

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But…

- The management of HIV-infected patients with lymphoma is frequently complicated by:
  - treatment-induced immunosuppression (e.g. neutropenia)
  - co-morbid disease (e.g. opportunistic infections)
  - drug interactions (e.g. chemotherapy and anti-retroviral therapy)

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cART during chemotherapy

Continue cART or discontinue cART during chemotherapy?

- Some clinicians recommend continuing cART during chemotherapy. Some don't…
- Concomitant administration of cART and chemotherapy has been shown to reduce the incidence of opportunistic infections and improves overall survival/complete response.

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cART during chemotherapy

Study	No/type of patients	Outcome
Cortes et al. Cancer 2002[6]	13 patients Prospective study investigating the use of hyper-CVAD in patients with HIV-related Burkitt Lymphoma	Nine out of 13 patients were on cART during chemotherapy. All four patients who did not receive cART died
Antinori et al. AIDS 2001 [7]	44 patients Retrospective study in patients who received CHOP/m-BACOD for HIV-related NHL	Virological response to cART was the only factor independently associated with complete response following chemotherapy
Vaccher et al. Cancer 2001 [8]	104 patients Retrospective analysis of two prospective trials in patients with HIV-related NHL	Patients on CHOP plus cART had fewer opportunistic infections (18 vs. 52%, *p*=0.05) and longer OS (38 vs. 85%, *p*=0.001) compared to CHOP only arm
Hoffmann et al. AIDS 2003 [9]	203 patients Retrospective observational study- patients with AIDS-related lymphoma	Response to cART was associated with prolonged survival. Patients receiving cART were more likely to achieve CR (71% vs. 48%, *p=0.006)*
Barta et al. Blood 2013 [10]	1546 patients Systematic review of 19 prospective clinical trials-patients with HIV-related NHL	Concurrent use of cART with chemotherapy was associated with improved CR rates (OR 1.89, *P*=0.005) and a trend towards improved OS (HR 0.78, *P*=0.07)

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cART and chemotherapy drug interactions

- The likelihood of cART-chemotherapy pharmacokinetic drug interactions is high.
- Protease inhibitors (PIs) may increase the plasma concentrations of chemotherapy- increased toxicity and treatment delays
- Non nucleoside reverse transcriptase inhibitors (NNRTIs) may decrease the plasma concentrations of chemotherapy- decreased efficacy and treatment failure
- Many chemotherapy drugs are also metabolized by the CYP system.
- Pharmacodynamic drug interactions e.g. zidovudine (AZT) and chemotherapy may increase the risk of hematological toxicity.

Walubo A. Expert Opin Drug Metab Toxicol 2007;3(4):583-98

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Chemotherapy drugs and CYP 450

Drug	Metabolism	Interaction with PIs (more with ritonavir)	Interaction with NNRTIs
Cyclophosphamide	CYP2B6, 2C19 (active) CYP 3A4 (inactive, toxic)	↑Via CYP2B6 induction ↑CYP3A4 inhibition	↑Via CYP2B6 induction
Etoposide	CYP3A4	↑via CYP3A4 inhibition	↓Via CYP3A4 induction
Vincristine/vinblastine	CYP3A4	↑↑via CYP3A4 inhibition	↓Via CYP3A4 induction
Doxorubicin	CYP3A4 involved in free radical generation in vitro.	May ↑ reduction via CYP2B6 induction to free radical and hence ↑ antineoplastic properties	May↑ reduction via CYP2B6 induction to free radical and hence ↑ antineoplastic properties
Prednisolone	CYP3A4	↑via CYP3A4 inhibition	↓ Via CYP3A4 induction

↑= increase in the concentration of the active metabolite
↓= decrease in the concentration of active metabolite

Antoniou T, Tseng AL.Clin Pharmacokinet 2005;44(2):111-45.

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cART and Chemotherapy Drug Interactions-Lessons learnt

- PI-based regimens were significantly associated with more treatment related toxicities compared to non-PI based regimens.
- Patients on PI-based regimens were less likely to complete their stage appropriate chemotherapy treatment.
- PI-based regimens should be used with extreme caution with vinca alkaloids. (avoid or chemotherapy dose reduction is warranted).
- Zidovudine use should be avoided in patients treated with chemotherapy due to the significant increase in the risk of haematological toxicities.

Vaccher et al. Cancer 2001;91(1):155-63.
Bower et al. Blood 2004;104(9):2943-6.
Ibrahim K, Milliken S. Blood. 2013;122(21):3843.

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Take Home Messages

- The advent of cART has completely changed the picture for HIV-associated lymphomas.
- Major improvements in the outcomes of HIV-associated lymphomas have been reported. Outcomes are now parallel to that observed in the HIV-negative patients.
- Current evidence supports concurrent use of cART with chemotherapy for HIV-associated lymphoma.
- If appropriate, non-PI based regimen should be considered during chemotherapy for HIV-associated lymphoma to minimize treatment-related toxicities.
- Avoid AZT with chemotherapy.

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Audience Response Question #1

- Which of the following is TRUE regarding the treatment of HIV-associated lymphoma

A. Introduction of cART had minimal effect on outcomes of HIV-associated lymphoma
B. Zidovudine should be used concurrently with chemotherapy for HIV-associated lymphoma
C. Current evidence supports ceasing cART during chemotherapy for HIV-associated lymphoma
D. Treatment outcomes of HIV-associated lymphoma are now similar to those observed with HIV negative patients

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HCT and HIV

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HCT and HIV

- In the HIV-negative setting, both autologous and allogeneic HCT have become well-established therapeutic options for the treatment of various hematological malignancies
  - Patients in remission but are at risk of relapse
  - Patients with relapsed/refractory disease
- HIV+ve patients on cART are better able to tolerate chemotherapy and results of treatment are similar now to non-HIV infected patients
- Consequently the use of HCT have been investigated in the post cART era

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HCT and HIV
Autologous HCT

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Autologous HCT

- First case report 1996, Gabarre et al, BMT.
- 40 year old male with NHL given BEAM (Carmustine, Etoposide, Cytarabine and Melphalan) conditioning.
- Multiple opportunistic infections (OI), including cytomegalovirus (CMV), *Mycobacterium avium* Complex (MAC) and cryptosporidiosis.
- Patient died but confirmed possibility of stem cell collection and engraftment.
- Post cART
  - 6 non-randomized studies
  - 2 cohort studies have compared HIV+ to non-HIV

Gabarre et al. BMT 1996;18:1195-7

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Autologous HCT for HIV-associated Lymphoma

Study	Failure to mobilise	Patients (n)	Tx related mortality	Median f/u (months)	Overall Survival (%)
Krishnan et al. Blood 2005 [11]	0	20	5%	32	85
Spitzer et al. BBMT 2008 [12]	2	20	5%	6	74
Re et al. Blood 2009 [13]	4	27	0	44	75
Gabarre et al. Haematologica 2004 [14]	NR*	14	0	36	71
Serrano et al. EBMT meeting 2010 [15]	0	33	0	61	61
Balsalobre et al. JCO 2009 [16]	NR*	68	7.5%	32	61

***NR= not reported**

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Autologous HCT for HIV-associated lymphomas

Study	Antiretroviral Therapy	CD4 cells/ul	Neutropenic infection	Late Complications
Gabarre et al. Haematologica 2004 [14]	Yes	300 (77-534)	14/14 (100%) 1 gde 3	2 CMV reactivations, 2 deaths-1 liver cancer @25mths, -1 AIDS @ 16mths
Krishnan et al. Blood 2005 [11]	Yes	174 (30-500)	12/20 (60%)	1 CMV retinitis, 2 CMV viraemia, 1 aspergillus, 2 *Pneumocystis jirovecI* pneumonia (PJP), 2 VZV, 1 hepatitis C virus (HCV)
Serrano et al Exp Hematol 2005 [17]	Yes	186 (72-325)	11/11 (100%)	1 CMV viraemia, 2 VZV(1 fatal), 1 pneumonitis
Spitzer et al. BBMT 2008 [12]	Yes	203 (53-574)	6/20 (30%)	1 c.difficile, 3 CMV viraemia, 4 HSV, 1 UTI
Re et al. Blood 2009 [13]	Yes	218 (17-561)	12/27 (44%)	6 VZV, 2 candida, 4 CMV viraemia, 1 CMV retinitis
Balsalobre et al. JCO 2009 [16]	Yes - 95%	162 (8-1159)	NR	3 second malignancies, 7 deaths-2 HIV-related, 4-bacterial, 1 unknown

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Autologous HCT St Vincent's Hospital, Sydney

- 12 autologous HCT
  - 1x acute myeloid leukaemia (AML)
  - 4 x multiple myeloma (MM)
  - 4x Burkitt lymphoma (BL)
  - 1x plasmablastic lymphoma
  - 1x primary effusion lymphoma (PEL)
  - 1x Hodgkin lymphoma (HL)
- ***No TRM, all patients continued cART during conditioning chemotherapy***
- 6 relapsed, 2 salvaged by allogeneic HCT, 2 MM salvage Rx
- 1 bacterial endocarditis;1 Progressive multifocal leukoencephalopathy (PML) that resolved.
- Non-treatment related deaths (n=5)
  - 1 AZT- related lactic acidosis
  - 1 developed 2nd malignancy - HL
  - 1 relapsed AML; 2 relapsed MM
- Overall survival from 1-8 yrs

Source: Dr Sam Milliken, St Vincent's Hospital, Sydney , Australia 2013

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Autologous HCT for lymphoma HIV(n=29) vs. non-HIV (n=29)

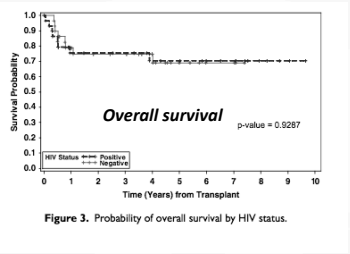

Figure 3. Probability of overall survival by HIV status.

Krishnan A et al. BBMT 2010; 16(9):1302–1308

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Autologous HCT for lymphoma

Outcome	HIV+ NHL (Case) N= 29	HIV- NHL (Control) N=29
Days to reach neutrophil count of > 0.5 x10^9/L	10 (5-19)	11 (9-35)
Total number of infections	28	14
Bacterial	17	11
Fungal	0	1
Viral	1	1
OI (CMV, Varicella zoster virus [VZV])	4	0
Unclassified §	6	1

§Unclassified: no organism could be isolated

Krishnan A et al. BBMT 2010; 16(9):1302–1308

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Immune Reconstitution after autologous HCT

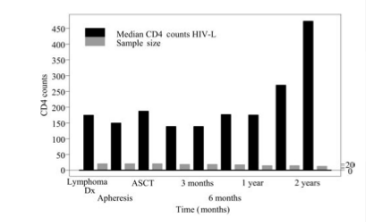

Figure 1. Median CD4 count trends during apheresis and after ASCT.

Krishnan A et al. BBMT 2010; 16(9):1302–1308

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Autologous HCT for HIV-associated lymphoma
Poor Prognostic Features

- Not achieving CR
- Chemo-resistant disease prior to HCT
- > 2 prior treatments
- Marrow involvement, stage IV
- Poor performance status
- CD4 count < 100 cells/µL
- NHL other than DLBCL
- Recent opportunistic infections
- High HIV DNA levels
- Hepatitis co-infection did not adversely affect results

Re A et al. Blood. 2009;114(7):1306-1313
Gabarre J al. Haematologica. 2004;89(9):1100-1108
Bortolin et al, 2010. AIDS Research and Human Retroviruses 26(2): 245-251

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Stem Cell Mobilization in HIV+ Patients

- HIV virus is known to alter the bone marrow microenviroment.
- cART is more likely to improve stem cell function/recovery if HIV viral load remains suppressed
- Consider continuation cART during high dose chemotherapy.
- Avoid zidovudine.
- G-CSF does not appear to exacerbate HIV replication (Michieli, et al Cell Transplantation;2011(20)3:351-370)

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Take Home Messages

- Autologous HCT is a feasible and effective option for HIV patients with hematological malignancies.
- Survival outcomes appear to be parallel to HIV-negative patients.
- Opportunistic infections are common, especially viral infections.
- CD4+ counts recover after 6-12 months post HCT.
- Continue cART
- Avoid zidovudine during high dose chemotherapy/mobilization.

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Audience Response Question #2

- Which of the following is NOT considered a poor prognostic feature for patients undergoing autologous HCT for HIV-associated lymphoma?

A. Poor performance status
B. Undetectable HIV viral load at HCT
C. CD4 count < 100cells/μL
D. Chemotherapy resistant diseases prior to HCT

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HCT and HIV Allogeneic HCT

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Allogeneic HCT for HIV-associated haematological malignancies

- Greater challenges
  - chronic immunosuppression
  - risk of opportunistic infections
  - complex drug interactions
- Success with solid organ transplantation
  - allayed concerns regarding chronic immunosuppression
  - HIV viral load could still be controlled by cART
  - drug interactions due to cytochrome P-450 (CYP) inhibition by certain antiretrovirals were managed by dose adjustments of calcineurin inhibitors.

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Allogeneic HCT- Literature Case Reports

- Since the introduction of cART there have been increasing reports of successful allogeneic HCT.
- Since 2000 increasing use of reduced intensity conditioning (RIC).
- Little data on immune reconstitution post transplant but it appears not too different from the HIV negative population.
- Almost all cases continue cART and engraftment does not appear impaired. Opportunistic infections do not appear increased.
- ? may have a secondary benefit in reducing the pool of latent HIV-infected lymphocytes.

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Allogeneic HCT
CIBMTR retrospective review

	Patients (n)	Disease	Donor	Conditioning	cART	Survival @ 59mths
Pre-1996	14	6 NHL 6 AML 2 non-haem	13 sib 1 MUD	All Myeloablative conditioning (MyAb)	None	2/14 14%
Post-1996	9	4 CML 4 NHL 1 AML	6 sib 3 MUD	6 MyAb 3 Reduced Intensity Conditioning (RIC)	8	4/9 44%
Overall	23					6/23 26%

Gupta V et al: BBMT 2009, 15:864–871

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Allogeneic HCT
case reports of myeloablative HCT + cART

Author	Disease	Donor	GVHD	Survival
Schlegel et al. JAIDS 2000 [18]	CML	sibling	limited	Alive @3 years
Sora et al. Exp Hematol 2002 [19]	AML	MUD	Grade II	Alive@42months
Tomonari et al. BMT 2005[20]	ALL	Cord	None	Alive@15months
Polizotto et al. BMT 2010 [21]	AML	MUD	none	Died @ 2yr CRF
Serrano et al. Blood 2008 [22]	ALL	Sibling	Grade III	Died @ 36months
Hutter et al. NEJM 2009[23]	AML	MUD	Grade 1	Alive @5years

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Allogeneic HCT
case reports of non-myeloablative HCT + cART

Author	Disease	Donor	GVHD	Survival
Kang et al. Blood 2002 [24]	HL	sibling	acute grade II	Dead @ 12 months
Kang et al. Blood 2002 [24]	AML	Sibling	Acute grade II	Alive @24 months
Woolfrey et al. Blood 2008 [25]	AML	MUD	Acute grade III	Dead@10months
Woolfrey et al. Blood 2008 [25]	AML	sibling	none	Alive @6months
Bryant & Milliken BBMT 2010 [26]	NHL- PEL	sibling	none	Alive@8 years
Milliken. St Vincent's Hosp, Sydney 2010	NHL Plasmablastic	MUD	Extensive cGVHD	Alive@ 4 years
Milliken. St Vincent's Hosp, Sydney 2011	AML	MUD	acute grade I	Alive@ 2 years

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Immune reconstitution after allogeneic HCT

- In autologous SCT-HIV+ patients on cART - CD4+ counts recover after 6-12 months similar to HIV negative patients.
- The literature on allogeneic transplantation in HIV- positive patients is much more sparse.
- Data in the non-HIV population suggest that the rate of immune reconstitution after transplant is dependent on factors
  - type of conditioning regimen
  - development of graft versus host disease (GVHD).

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Audience Response Question #3

- Which of the following is TRUE regarding the use of allogeneic HCT for HIV-infected patients with hematological malignancies.

A. Allogeneic HCT is a feasible option for HIV-infected patients with high risk hematological malignancies
B. GVHD seems to be minimal with HIV patients due to impaired immunity.
C. Continuation of cART during HCT is generally NOT recommended
D. The risk of opportunistic infections is generally very low

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Pharmaceutical Considerations for HIV patients undergoing HCT

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cART during HCT

- No evidence that concomitant cART adversely affects transplant outcomes –continue cART but watch for drug interactions!
- AZT use should be avoided in patients undergoing HCT due to the significant increase in the risk of hematological toxicities and potential delay in engraftment.
- PIs and NNRTIs are substrates and potent inhibitors or inducers of the CYP-450 system.
  (e.g. CYP3A4 inhibition by ritonavir ➔ Potential increase in the toxicities of cyclosporin, tacrolimus and sirolimus)

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Metabolism of some commonly used Antiretroviral agents

Antiretroviral Agent	Class	Metabolism
Tenofovir	**Nucleos(t)ide reverse transcriptase inhibitor (NRTI)**	Minimal systemic metabolism (renal excretion 70-80%)
Emtricitabine		Minimal systemic metabolism. (renal excretion 86%)
Abacavir		Hepatic elimination with no known effect on CYP450
Efavirenz	**Non-nucleoside reverse transcriptase inhibitor (NNRTI)**	Potent inducer and inhibitor of CYP3A4. Efavirenz induces CYP2B6 and UGT1A1. Also inhibits CYP2C9 and 2C19.
Nevirapine		Substrate and a potent inducer of CYP3A4 and 2B6 enzymes
Etravirine		Weak inducer of the CYP3A4 and CYP2B6. Weak inhibitor of CYP2C9 and moderate inhibitor of CYP2C19
Atazanavir	**Protease inhibitors (PI)**	Inhibits CYP3A4 and UGT1A1
Darunavir		Primarily metabolised by CYP3A4. Inhibits CYP3A4
Ritonavir		Potent inhibitor of CYP enzymes in the following order 3A4>2D6>2C9>2C19 Induces:CYP1A2,CYP2B6,CYP2C9/2C19 and glucoronyl transferases
Raltegravir	**Integrase inhibitor (INSTI)**	Glucuronidation (UGT1A1) and has no inhibitory or inductive potential in-vitro

UGT= Uridine diphospho-glucuronosyl transferase

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cART during HCT

- Integrase-inhibitors (e.g. raltegravir) based regimens appears safe to use-minimal drug interactions.
- CCR5-antagonists (maraviroc). Maraviroc is a substrate for CYP3A4 and has no potential to induce or inhibit CYP450.
- Mucositis , nausea and vomiting
  - Some PIs needs to be taken with food e.g. darunavir, atazanavir, ritonavir
  - Stopping cART can lead to monotherapy e.g. antiretrovirals with long half-life (efavirenz)
- Added renal toxicity:
  - Calcineurin inhibitors and tenofovir
- Supportive-therapy-cART drug interactions e.g. (acid suppressants, antifungals and corticosteroids).

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Other considerations

- Antifungal prophylaxis
- PJP & toxoplasmosis prophylaxis§
- Antiviral prophylaxis (HSV/VZV)
- MAC prophylaxis if required (CD4-cell count < 75 cells/μL)
- CMV monitoring until day+100
- Monitoring of Viral load, CD4+ cell count closely after transplant.
- Role for therapeutic drug monitoring (TDM) of cART

§Consider using > 4 Double Strength (DS) tablets of cotrimoxazole per week.

Ribera et al. CID1999;29:1461–6.

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Audience Response Question #4

- Which of the following antiretroviral agents would be less likely to contribute to drug interactions with common immunosuppressant agents used in HIV patients undergoing allogeneic stem cell transplants.

A. Atazanavir/ritonavir
B. Efavirenz
C. Raltegravir

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Case Study

- February 2010 - 56yr-old male referred for consideration of allogeneic HCTx
- 2004 - Large B-cell NHL, Rx with R-CHOP X 6
- March 2009 - secondary MDS/AML 'erythroleukemia' with normal cytogenetics - in first remission (induction chemotherapy and consolidation with HiDAC (high dose cytarabine x2 cycles)
- Good performance status.
- HIV Dx 2002, well controlled:
  - Tenofovir/emtricitabine/(TDF/FTC) once daily+ lopinavir/ritonavir (LPV/r) 400mg/100 mg twice daily
  - CD4 250 cells, HIV-viral load undetectable, no other AIDS diagnosis.
- Elected not to have MUD HCT

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Case Study

- October 2010 - AML relapse
- 'self-referred' February 2011
- 2nd remission after re-induction and consolidation chemotherapy
- 44yr old male MUD identified
- May 2011 Fludarabine /Melphalan RIC bone marrow HCT
- Discharged well Day+ 21, no major early complications

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Case Study

- Only needed cyclosporin 20 mg once a day (level 158ug/L) and itraconazole 100mg/day (level 1752ug/L) as continued cART (TDF/FTC + LPV/r)
- Post-HCT prophylaxis with cotrimoxazole, valaciclovir and azithromycin.
- Full donor chimaerism
- Day+46 cutaneous GVHD grade 2, settled with prednisone 25mg twice daily.
- CD4 counts; 270 cells/μL pre-HCT; 36 cells/μL @ 3months; 104 cells/ μL@ 6months
- HIV viral load consistently 'not detected'

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Case Study

- Dec 2012 - admitted with neutropenic sepsis
- Bone marrow biopsy - AML in remission
- Cultures all negative, neutropenia spontaneously recovered
- ? Viral infection
- Jan 2012 - ataxia, diplopia x 1 week
- CT – Space occupying lesion L frontal lobe @ grey/white matter junction ? abscess
- Negative CMV PCR, Toxoplasma serology, adherent to co-trimoxazole (1 DS tablet (800mg/160mg) three times a week) , CD4 104 cells/µL, HIV-VL undetectable
- Condition rapidly deteriorated - comatose, ICU

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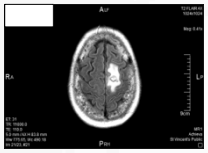
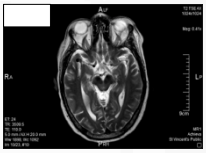
Case Study





- MRI - multiple rim-enhancing lesions both hemispheres, R basal ganglia, midbrain and cerebellum

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Case Study

- Bx of L frontal lesion - CEREBRAL TOXOPLASMOSIS
- PCR positive
- Serum testing remains negative @ 2months
- Rx - triple Rx with Clindamycin (6wks), Pyrimethamine (6wks-pancytopenia), Sulfadiazine (1wk-rash) followed by Atovaquone maintenance. Levetiracetam for seizures
- H. zoster L scalp despite prophylactic valaciclovir (500mg BID)
- Chest infection
- Excellent recovery, D/C to rehab after 2 months, home @ 3 months, walks with a stick, eye patch

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Conclusions

- Autologous HCT is an acceptable and safe strategy to salvage patients with relapsed/resistant NHL/HL-results similar to non-HIV infected population.
- Limited data for allogeneic transplantation in the post cART era but reasonable early results justifies its continued use. ? non-myeloablative protocols.
- Immune reconstitution is similar to non-HIV patients for autologous HCT and appears satisfactory for allogeneic HCT, however opportunistic infections may be more common mandating careful post-HCT surveillance.
- cART may be continued to help optimize immune recovery- Watch drug interactions!

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Best approach

- Therefore multidisciplinary cooperation between oncologists, HIV physicians and clinical pharmacists with expertise in oncology and HIV is needed to ensure that HIV patients with malignancies/presenting for HCT are suitably managed.

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Sydney World AIDS Day

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QUESTIONS?

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