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The exclusion of people living with HIV from clinical trials in lymphoma:

Prejudice or justified?

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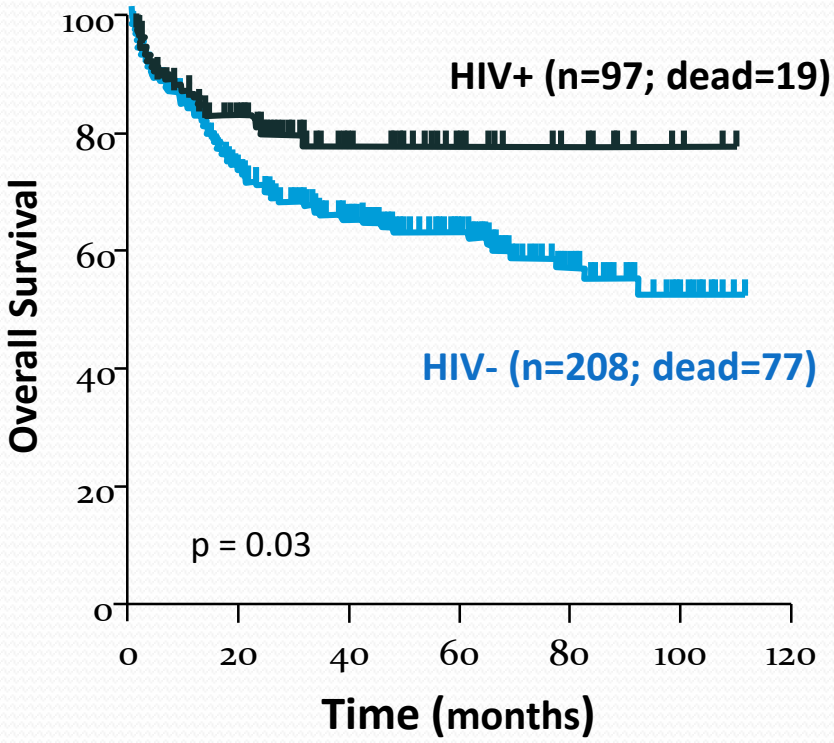
Background

The incidence of both Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) is higher in people living with HIV (PLWH)

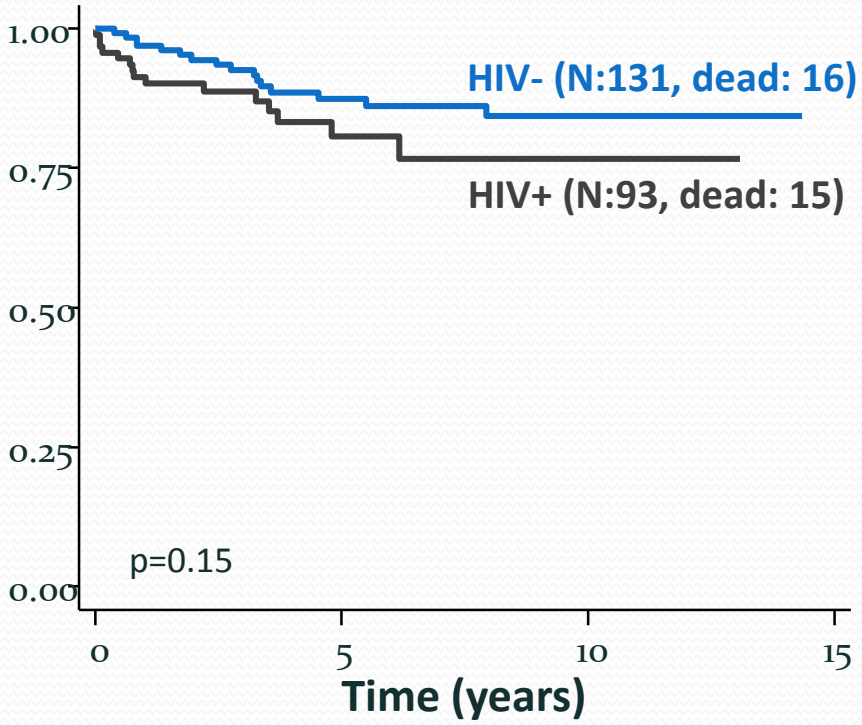
Since the introduction of cART, the outcome of HL & NHL has dramatically improved with survival equivalent to that observed in the HIV negative population

DLBCL overall survival



Coutinho R, AIDS. 2014; 28: 689-697

Hodgkin's Disease overall survival



Montoto S, J Clin Oncol. 2012, 30:4111-6

Background

BHIVA Guidelines (2014) recommend to treat patient with HIV and HL/NHL with the same chemotherapy protocols used in the HIV negative population

PLWH may benefit from complex and novel cancer treatments therefore should be evaluated for inclusion in cancer clinical trials

Background

PLWH are at increased risk for:

(i) Immunosuppression toxicity during chemotherapy

(ii) Pharmacokinetic interactions between ARVs and chemotherapeutic agents

Objectives

1. Evaluate whether PLWH are excluded from clinical trials in lymphoma in UK
2. Evaluate whether a clear justification for exclusion is offered in the protocols
3. Assess if increased risk of immunodeficiency can justify exclusion PLWH
4. Assess if pharmacokinetic interactions can justify exclusion PLWH

Methods

Identification of all open clinical trials in lymphoma in United Kingdom in January 2015 and their inclusion and exclusion criteria via the UK Clinical Research Network Study Portfolio website

Evaluation of the mechanism of action, toxicity, metabolism and pharmacokinetic interactions of the studied drugs through protocols, product information sheets and published data

Results

1) Exclusion of PLWH from clinical trials in lymphoma

56 multicentre open clinical trials in lymphoma

10 Exclusively observational trials

46 Interventional (45)/ interventional and observational (1)

PLWH eligible for 14/46 (30%)

1 Only if HIV VL<50 (undetectable)

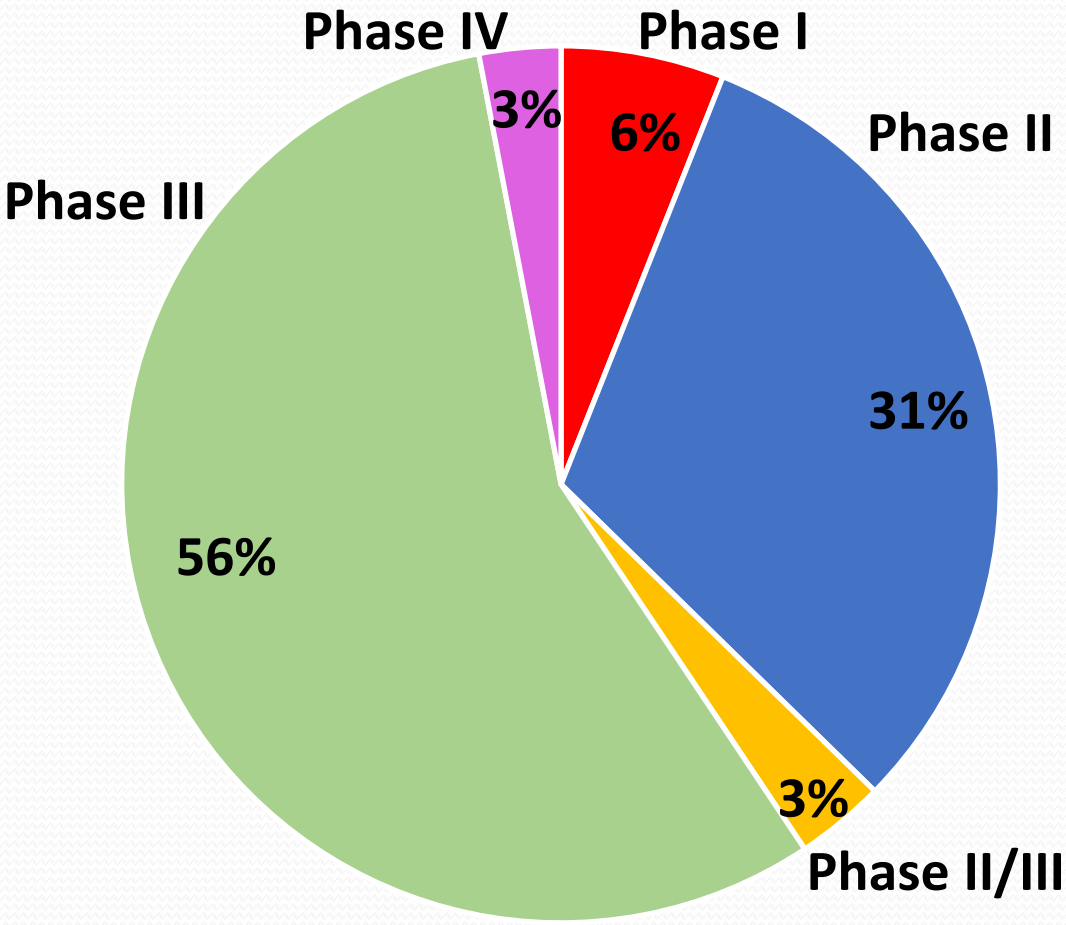
13 No specification

PLWH excluded from 32/46 (70%)

6/32 trials did not specify an HIV test at screening visit

Results

2) The 32 clinical trials excluding PLWH: study phase



Results

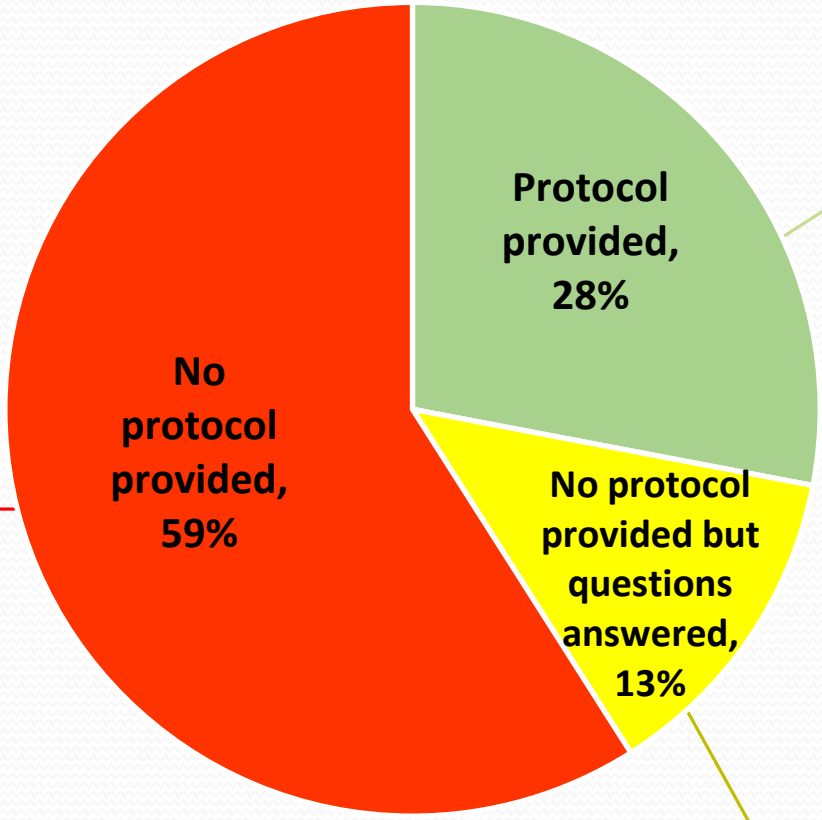
3) The 32 clinical trials excluding PLWH: novel drugs/novel treatment investigated

1) Monoclonal antibodies	*13 trials*
2) Cytotoxic agents	*5 trials*
3) Bruton tyrosine kinase inhibitors	*4 trials*
4) Proteasome inhibitors	*3 trials*
5) PIK3 inhibitors	*2 trials*
6) Serine/threonine protein kinase inhibitors	*1 trial*
7) Bcl-2 inhibitors	*1 trial*
8) Monocarboxilate transporter	*1 trial*
+	
- Efficacy of Herpes Zoster vaccine	*1 trial*
- Efficacy of surgery only	*1 trial*

Results

4) Was a scientific justification provided in the protocol?

"Unfortunately, I cannot supply you with any protocols as they are confidential commercial documents which are only available to investigators participating in the studies"



No justification provided in the protocol

1) "to mitigate against any safety risks for these patients through risk of infection"
2) "we do not specifically outline the reason why we have excluded HIV patients"
3) "there isn't a specific reason" "good point you have raised"
4) "the protocol would not supply answer to your query" "unable to help further with your query"

Results

5) Assessment of increased risk of immunosuppression:

Increased risk of toxicity identified in 2 clinical trials:

1) Trial: "*A Cancer Research UK Phase I Trial of AZD3965, a monocarboxylate transporter 1 inhibitor (MCT1) in patients with advanced cancer*"
MCT1: potent immunosuppressor which blocks T lymphocyte proliferation.

2) Trial: "*Alisertib vs Investigator's Choice (Selected Single Agent - pralatrexate or gemcitabine or romidepsin) in relapsed or refractory peripheral T-cell lymphoma*"

Romidepsin: histone deacetylase inhibitor which has been demonstrated to be a potent activator of latent HIV ex vivo.
But investigator may choose the other two options.

No increased risk of toxicity identified for the other 30 trials

Results

6) Assessment of pharmacokinetic interactions between ARVs and chemotherapeutic agents:

Potential pharmacokinetic interaction between ARVs and investigational agents/compared standard treatment identified in 88% trials

Chemotherapeutic agents metabolised by the same cytochromes potentially affected by ARVs (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP3A4/5, …)

No risk of pharmacokinetic interaction was found in 12% trials

1) Monocarboxilate transporter trial (phase I study)
2) Anti-CD19 DI-B4 monoclonal antibody trial (phase I study)
3) Rituximab plus Lenalidomide versus Rituximab
4) Efficacy of Herpes Zoster vaccine Trial

Conclusion

For most clinical trials there does not appear to be a justification for excluding PLWH.

Clear justification for excluding PLWH is not provided in the available protocols.

Immunosuppression by anti-lymphoma agent found in only 6% trials.

Selection of ARVs (avoiding boosted PIs) would enable eligibility with no risk of drug interactions.

Our study shows that PLWH could potentially access a large number of lymphoma trials with personal and scientific medical benefit.

Thank you for your attention!