4th INTERNATIONAL CONGRESS

# Viral Infections in Immunocompromised Patients

Trapianto di cellule staminali in pazienti con infezione da HBV e HCV

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Division of Gastroenterology
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University of Torino, Italy

# Outline

- HBV
  - **Auto-HSCT**
    - Overt carrier
    - Anti-HBc positive
  - **Allo-HSCT**
    - Overt carrier (Donor)
    - Overt carrier (Recipient)
    - Anti-HBc positive (Donor)
- HCV
  - **Auto-HSCT**
    - Overt carrier (HCV RNA positive)
    - Sieropositive (HCV RNA negative)
  - **Allo-HSCT**
    - Overt carrier (Donor)
    - Overt carrier (Recipient)

Clinical Practice Guidelines

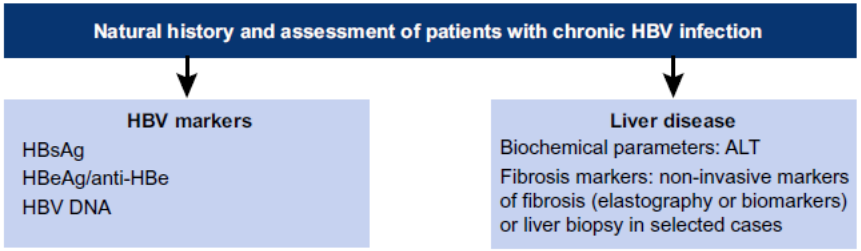
CrossMark

EASL JOURNAL OF HEPATOLOGY

# EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection☆

European Association for the Study of the Liver*

Journal of Hepatology **2017** vol. 67 | 370–398




| | HBeAg positive | | HBeAg negative | |
|---|---|---|---|---|
| | Chronic infection | Chronic hepatitis | Chronic infection | Chronic hepatitis |
| HBsAg | High | High/intermediate | Low | Intermediate |
| HBeAg | Positive | Positive | Negative | Negative |
| HBV DNA | >$10^7$ IU/ml | $10^4$-$10^7$ IU/ml | <2,000 IU/ml°° | >2,000 IU/ml |
| ALT | Normal | Elevated | Normal | Elevated* |
| Liver disease | None/minimal | Moderate/severe | None | Moderate/severe |
| Old terminology | Immune tolerant | Immune reactive HBeAg positive | Inactive carrier | HBeAg negative chronic hepatitis |

**Fig. 1. Natural history and assessment of patients with chronic HBV infection based upon HBV and liver disease markers.** *Persistently or intermittently. °°HBV DNA levels can be between 2,000 and 20,000 IU/ml in some patients without sings of chronic hepatitis.

## HBV phases

1 e+ CI

2 e+ CH

3 e- C I

4 e- CH

5 OBI*

anti-HBc positive

# Haematology and HSCT


## WHAT IS THE RISK OF REACTIVATION?

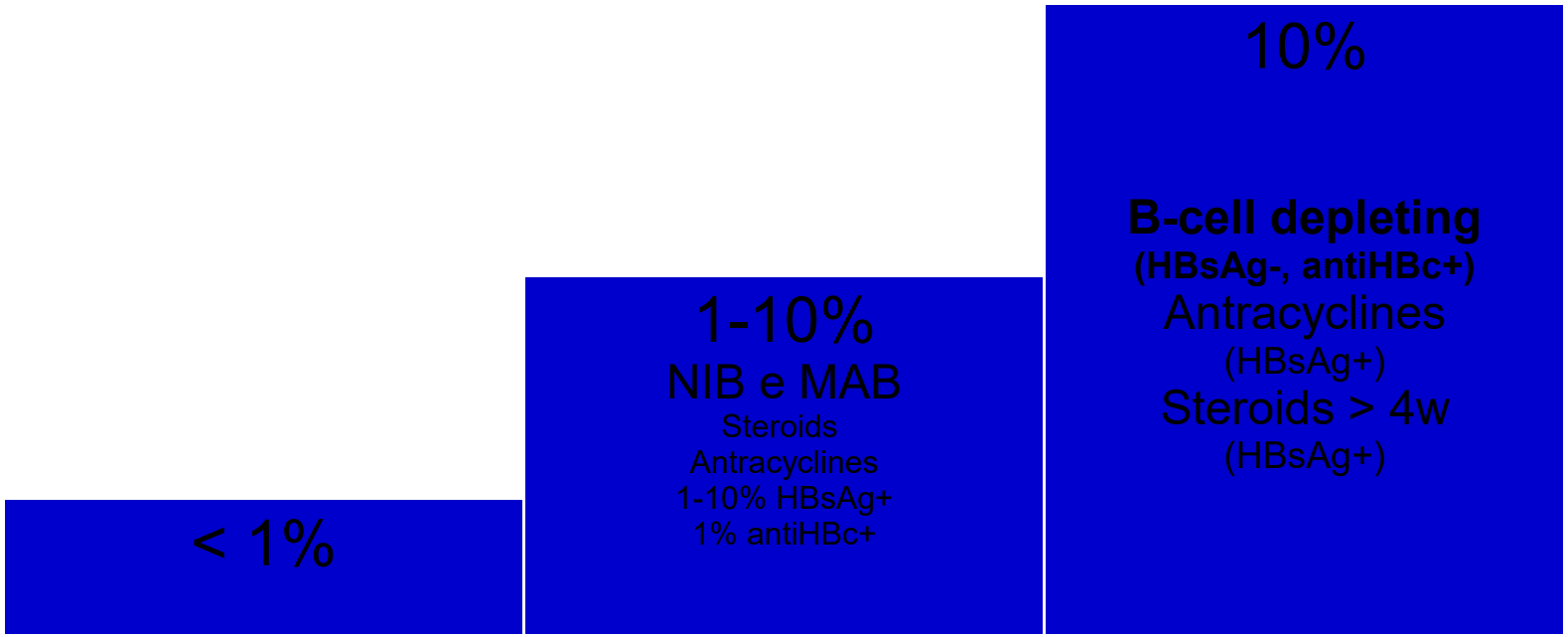
**Statements.**

1. HBsAg positive: median 50% (range 24-88%)(GRADE 1B);

2. HBsAg negative/antiHBc positive undergoing rituximab treatment (median 16.9%; range 13.1-21.9 ) or allo-HCT (14-86%) (GRADE 1B)

# HBV
# Risk of reactivation in HSCT

HSCT




RP Perrillo et al. Gatroenterology 2015; 48: 221-24; Loomba Gastroenterology2017; www.webaisf.com 2017

# HBV
# auto-HSCT

# Haematology and auto-HSCT


## WHO SHOULD BE TREATED AND HOW?

**Statements.**

- HBsAg positive: ETV or TDF (1B) or TAF(1C);
- anti-HBc positive (all): LAM (1B)

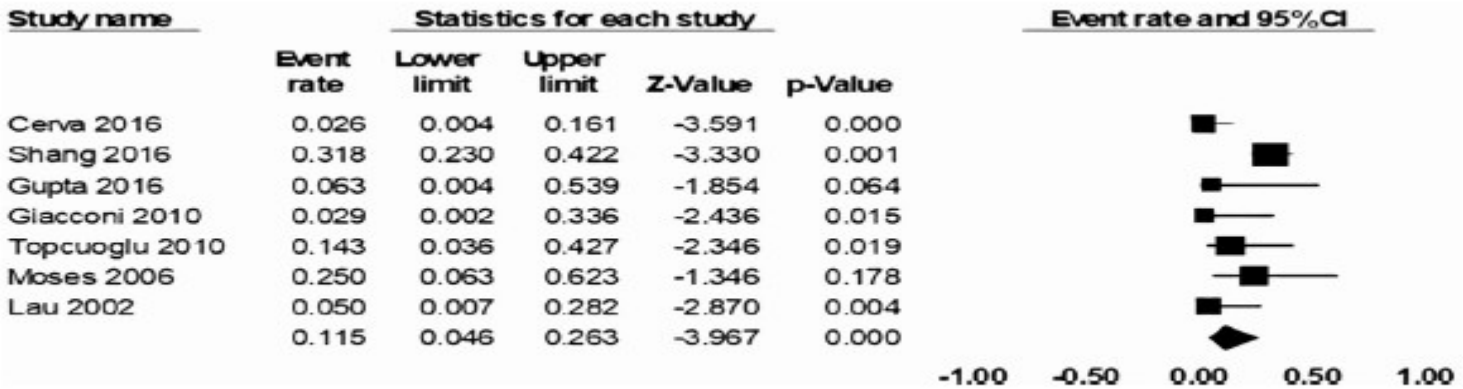
1 **Sì**

**Vote in favour: 98,1%**

2 **No**

# Prophylaxis for Hepatitis B Virus Reactivation after Allogeneic Stem Cell Transplantation in the Era of Drug Resistance and Newer Antivirals: A Systematic Review and Meta-Analysis

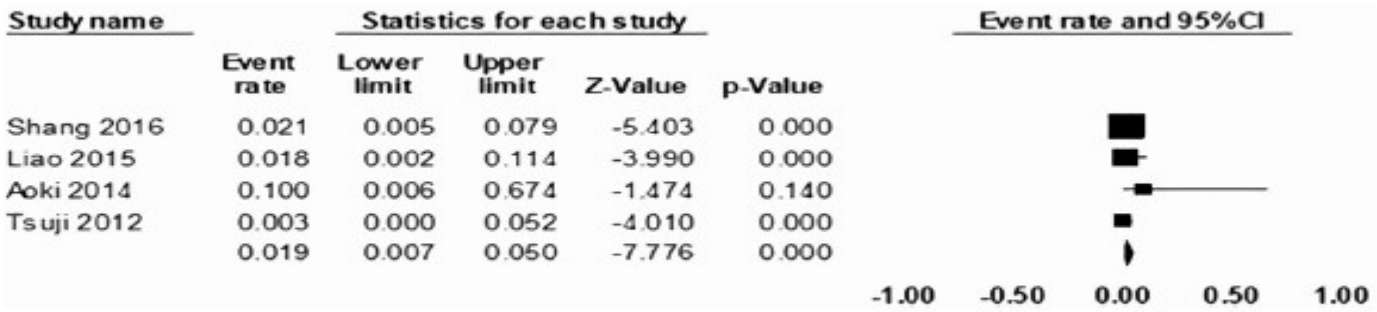
Aida Siyahian [1], Saad Ullah Malik [2], Adeela Mushtaq [2], Carol L. Howe [3], Aneela Majeed [4], Tirdad Zangeneh [4], Samar Iftikhar [5], Shahid Habib [6], Umar Zahid [2,7], Irbaz Bin Riaz [8], Zahib Warraich [2], Warda Faridi [2], Faiz Anwer [2,*]



| Study name | Event rate | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|
| Cerva 2016 | 0.026 | 0.004 | 0.161 | -3.591 | 0.000 |
| Shang 2016 | 0.318 | 0.230 | 0.422 | -3.330 | 0.001 |
| Gupta 2016 | 0.063 | 0.004 | 0.539 | -1.854 | 0.064 |
| Giacconi 2010 | 0.029 | 0.002 | 0.336 | -2.436 | 0.015 |
| Topcuoglu 2010 | 0.143 | 0.036 | 0.427 | -2.346 | 0.019 |
| Moses 2006 | 0.250 | 0.063 | 0.623 | -1.346 | 0.178 |
| Lau 2002 | 0.050 | 0.007 | 0.282 | -2.870 | 0.004 |
| | 0.115 | 0.046 | 0.263 | -3.967 | 0.000 |



**Figure 2.** Efficacy of LAM prophylaxis in preventing HBVr among allo-HSCT patients.



| Study name | Event rate | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|
| Shang 2016 | 0.021 | 0.005 | 0.079 | -5.403 | 0.000 |
| Liao 2015 | 0.018 | 0.002 | 0.114 | -3.990 | 0.000 |
| Aoki 2014 | 0.100 | 0.006 | 0.674 | -1.474 | 0.140 |
| Tsuji 2012 | 0.003 | 0.000 | 0.052 | -4.010 | 0.000 |
| | 0.019 | 0.007 | 0.050 | -7.776 | 0.000 |



**Figure 3.** Efficacy of ETV prophylaxis in preventing HBVr among allo-HSCT patients.

Original Investigation

# Entecavir vs Lamivudine for Prevention of Hepatitis B Virus Reactivation Among Patients With Untreated Diffuse Large B-Cell Lymphoma Receiving R-CHOP Chemotherapy

## A Randomized Clinical Trial

HBsAg+

He Huang, MD; Xueying Li, MD; Jun Zhu, MD, PhD; Sheng Ye, MD; Hongyu Zhang, MD; Wei Wang, MD; Xiangyuan Wu, MD; Jiewen Peng, MD; Bing Xu, MD; Yingcheng Lin, MD; Yabing Cao, MD; Haoran Li, MD, PhD; Suxia Lin, MD; Qing Liu, PhD; Tongyu Lin, MD, PhD

Patients enrolled in the parent study who were seropositive for the hepatitis B surface antigen and had normal liver function, serum HBV DNA levels of less than $10^3$ copies/mL, and no prior antiviral therapy were randomized to entecavir (n = 61) or lamivudine (n = 60).

| | Patients With Event, No. (%) | | | |
|---|---|---|---|---|
| | Entecavir (n = 61) | Lamivudine (n = 60) | Difference (95% CI), % | *P* Value |
| HBV-related hepatitis | 0 | 8 (13.3) | 13.3 (4.7 to 21.9) | .003 |
| HBV reactivation | 4 (6.6) | 18 (30.0) | 23.4 (10.2 to 36.6) | .001 |
| Chemotherapy disruption | 1 (1.6) | 11 (18.3) | 16.7 (6.4 to 27.0) | .002 |
| Treatment-related adverse events | 15 (24.6) | 18 (30.0) | 5.4 (−10.5 to 21.3) | .50 |
| Hepatitis B e antigen status | | | | |
| Seropositive | 20 (33) | 14 (23) | | |
| Seronegative | 41 (67) | 46 (77) | | |
| Hepatitis B core antibody status | | | | |
| Seropositive | 57 (93) | 60 (100) | | |
| Seronegative | 4 (7) | 0 | | |

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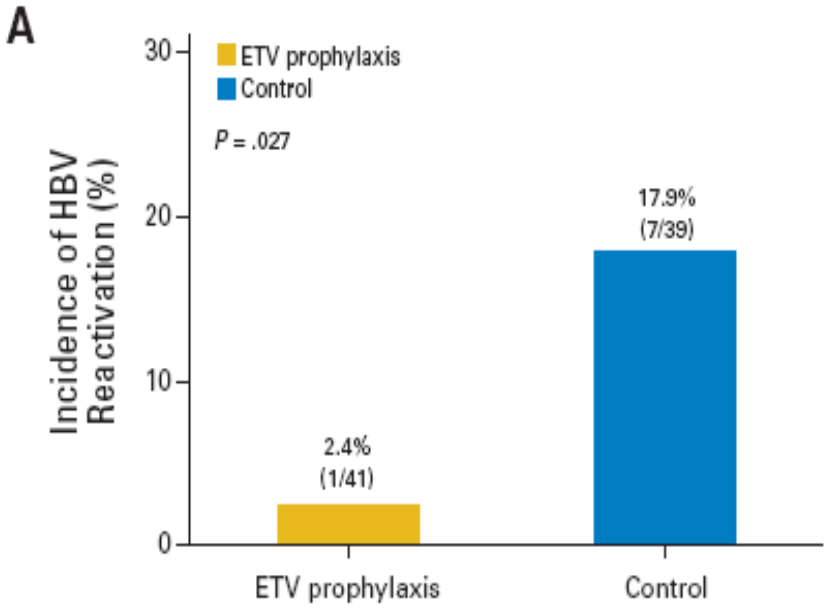
JOURNAL OF CLINICAL ONCOLOGY

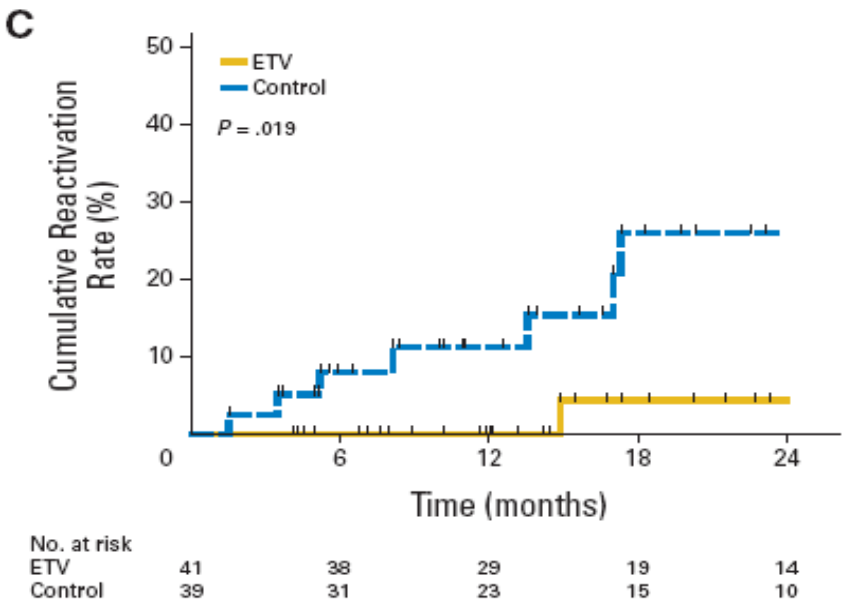
ORIGINAL REPORT

**AntiHBc+**

# Randomized Controlled Trial of Entecavir Prophylaxis for Rituximab-Associated Hepatitis B Virus Reactivation in Patients With Lymphoma and Resolved Hepatitis B

*Yi-Hsiang Huang, Liang-Tsai Hsiao, Ying-Chung Hong, Tzeon-Jye Chiou, Yuan-Bin Yu, Jyh-Pyng Gau, Chun-Yu Liu, Muh-Hwa Yang, Cheng-Hwai Tzeng, Pui-Ching Lee, Han-Chieh Lin, and Shou-Dong Lee*




37.5% HBV DNA pos (mean 42 IU); 64 ©-80 (T) % anti-HBs+; ETV 3 months after R-CHOP (mean fu 18m)

# Haematology and HSCT


## HOW LONG SHOULD BE TREATED AND/OR MONITORED?

- **Chronic Hepatitis and HBeAg-positive Chronic Infection:** long term-treatment should follow the **guidelines** regarding their immunocompetent counterpart (1B)
- **Anti-HBe positive Chronic Infection and anti-HBc positive:** prophylaxis should be continued **for at least 18 months** after the discontinuation of Immunosuppressive treatments (1 B)

1 **Sì**

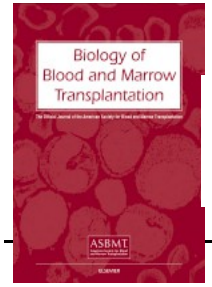
2 **No**

**Vote in favour: 100%**

# HBV
# allo-HSCT
# Donors

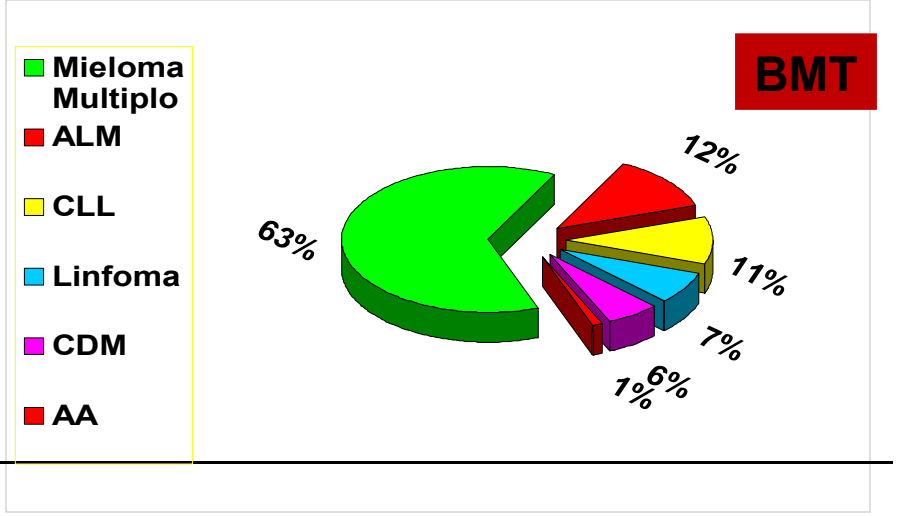
Title: Hepatitis B Virus Reactivation And Efficacy Of Prophylaxis With Lamivudine In Patients Undergoing Allogeneic Stem Cell Transplantation

Authors: Luisa Giaccone, Moreno Festuccia, Andrea Marengo, Isabel Resta, Roberto Sorasio, Fabrizia Pittaluga, Francesca Fiore, Mario Boccadoro, Mario Rizzetto, Benedetto Bruno, Alfredo Marzano




2010

*Biol Blood Marrow Transplant 16:809-817, 2010*




## 117 recipients

| N. | HBsAg | Anti-HBc before BMT | Donor | Proph. | Anti-HBc+ post-BMT | Hepatitis B |
|---|---|---|---|---|---|---|
| 87 | neg | neg | 82 Anti-HBc- | no | 0/82 | 0 |
| | | | 5 Anti-HBc+ | no | 1 | 0 |
| 25 | neg | pos | 3 anti-HBc+ | 11 LAM (>2005) | 7/11 (2 NA) | 0 |
| | | | 3 anti-HBc+ | 14 no (< 2005) | 10/14 (1 NA) | 3/14 (21%) |
| 3 | neg | 2 pos | 3 HBsAg+ | LAM | 3/3 | 0 |
| 2 | pos | pos | NA | LAM | 2/2 HBsAg- 3-13 m post-BMT | 0 |

# No increased mortality from donor or recipient hepatitis B- and/or hepatitis C-positive serostatus after related-donor allogeneic hematopoietic cell transplantation

M. Tomblyn[1], M. Chen[2], M. Kukreja[2], M.D. Aljurf[3], F. Al Mohareb[3], B.J. Bolwell[4], J.-Y. Cahn[5], M.H. Carabasi[6], R.P. Gale[7], R.E. Gress[8], V. Gupta[9], G.A. Hale[10], P. Ljungman[11], R.T. Maziarz[12], J. Storek[13], J.R. Wingard[14], J.-A.H. Young[15], M.M. Horowitz[2], and K.K. Ballen[16]

Iam

| Recipient | | | Donor | | | |
|---|---|---|---|---|---|---|
| HBsAg | HBcAb | HCAb | HBsAg | HBcAb | HCAb | N (%) |
| + | − | − | − | − | − | 28 (17) |
| − | + | − | − | − | − | 27 (17) |
| − | − | + | − | − | − | 29 (18) |
| − | − | − | + | − | − | 14 (12) |
| − | − | − | − | + | − | 7 (4) |
| − | − | − | − | − | + | 12 (7) |
| + | − | + | − | − | − | 1 (<1) |
| − | + | + | − | − | − | 6 (4) |
| − | − | − | − | + | + | 3 (2) |
| − | + | − | − | + | − | 8 (5) |
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| + | − | − | − | + | − | 7 (4) |
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| − | − | + | − | − | + | 5 (3) |
| − | + | + | + | − | − | 2 (1) |
| − | + | + | − | + | − | 1 (<1) |
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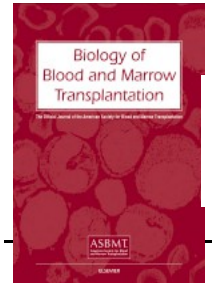


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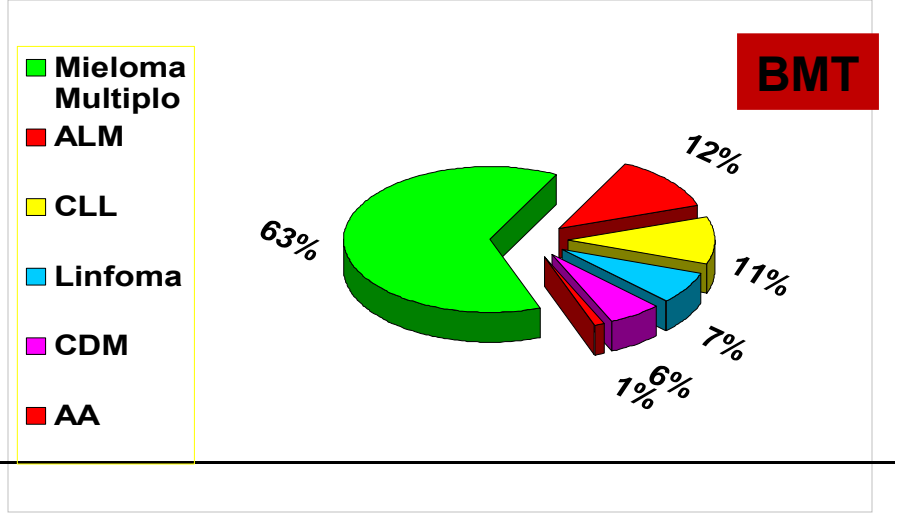


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# HBV
# allo-HSCT
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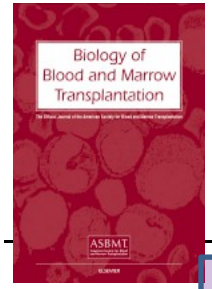


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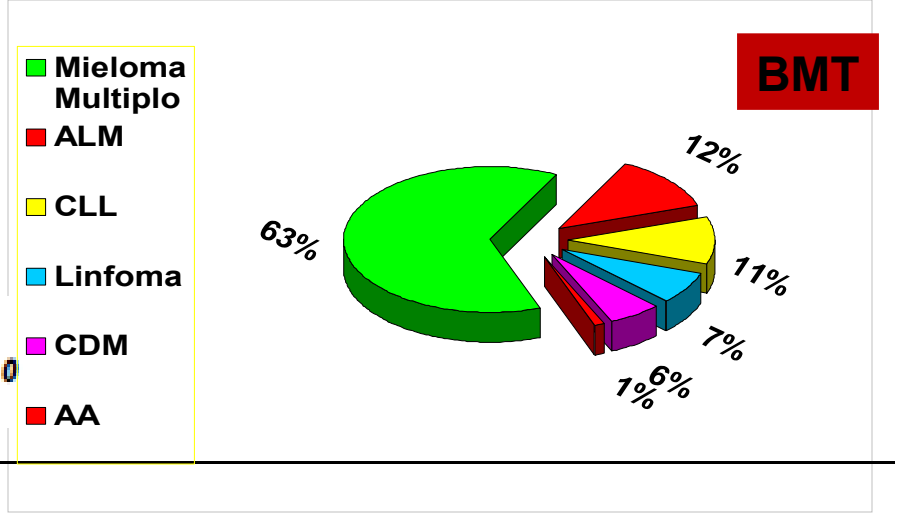


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| Recipient | | | Donor | | | |
|---|---|---|---|---|---|---|
| HBsAg | HBcAb | HCAb | HBsAg | HBcAb | HCAb | N (%) |
| + | − | − | − | − | − | 28 (17) |
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| − | − | + | − | − | − | 29 (18) |
| − | − | − | + | − | − | 14 (12) |
| − | − | − | − | + | − | 7 (4) |
| − | − | − | − | − | + | 12 (7) |
| + | − | + | − | − | − | 1 (<1) |
| − | + | + | − | − | − | 6 (4) |
| − | − | − | − | + | + | 3 (2) |
| − | + | − | − | + | − | 8 (5) |
| − | + | − | + | − | − | 3 (2) |
| + | − | − | − | + | − | 7 (4) |
| + | − | − | + | − | − | 7 (4) |
| − | − | + | − | − | + | 5 (3) |
| − | + | + | + | − | − | 2 (1) |
| − | + | + | − | + | − | 1 (<1) |
| − | + | + | − | − | + | 1 (<1) |

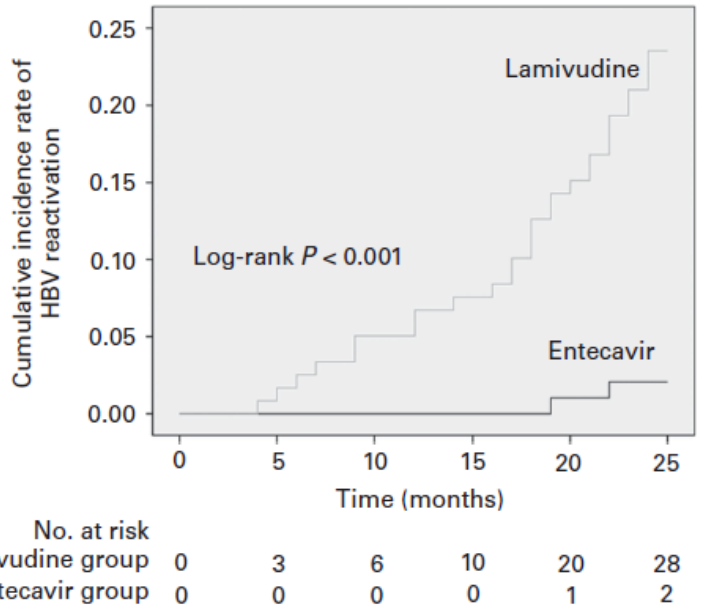
Categories of recipient and donor hepatitis B and hepatitis C serostatus in the 161 cases in this analysis

*Transpl Infect Dis*. Author manuscript; available in PMC 2013 October 01.

ORIGINAL ARTICLE

# A comparison of lamivudine vs entecavir for prophylaxis of hepatitis B virus reactivation in allogeneic hematopoietic stem cell transplantation recipients: a single-institutional experience

J Shang, H Wang, J Sun, Z Fan, F Huang, Y Zhang, Q Jiang, M Dai, N Xu, R Lin and Q Liu



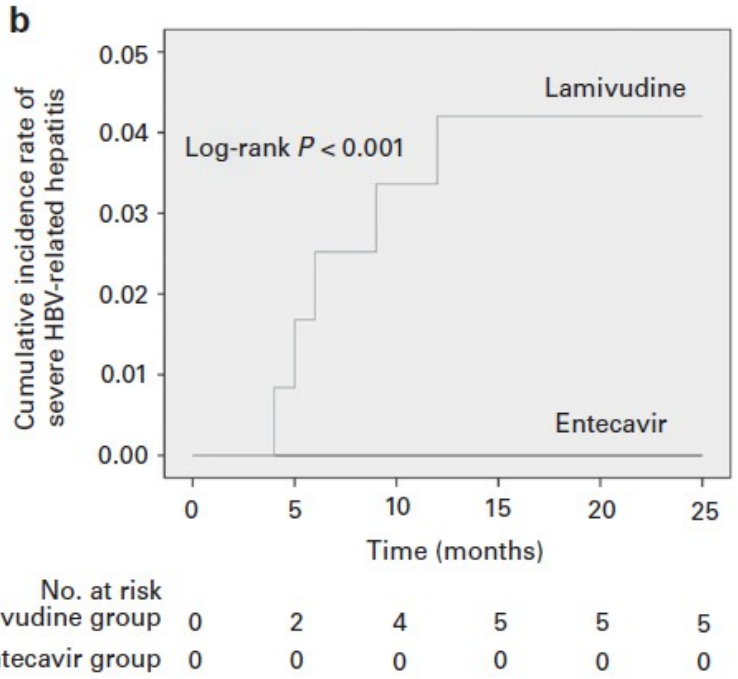




**Figure 1.** Cumulative incidence curves of HBV reactivation in the lamivudine and entecavir groups after allo-HSCT. Differences between cumulative incidence curves were tested by the log rank test. A full color version of this figure is available at the *Bone Marrow Transplantation* journal online.

# HCV
# auto-HSCT

# Haematology and HSCT


**WHAT IS THE RISK OF VIRAL REACTIVATION IN THE SPECIFIC SETTING?**

The overall risk of HCV reactivation in Hematology is 36% [95% CI: 22% - 50%] (GRADE B2)

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

# Hepatitis C Virus Infection in Patients Undergoing Hematopoietic Cell Transplantation in the Era of Direct-Acting Antiviral Agents

Andreas Kyvernitakis [1], Parag Mahale [1], Uday R. Popat [2], Ying Jiang [1], Jeff Hosry [1], Richard E. Champlin [2], Harrys A. Torres [1,*]

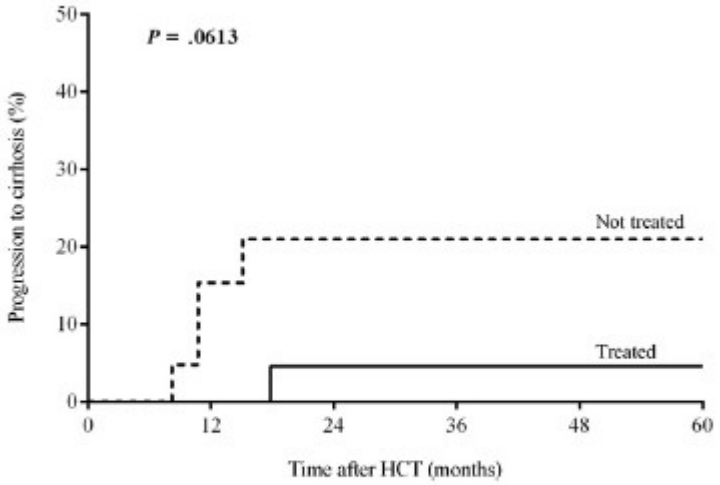



**Figure 1.** Cumulative incidence of progression of HCV infection to cirrhosis in cancer patients who received AVT versus those who did not. HCT recipients who received AVT had a trend toward a lower rate of progression to cirrhosis at 5 years (5% versus 21%; $P = .06$).

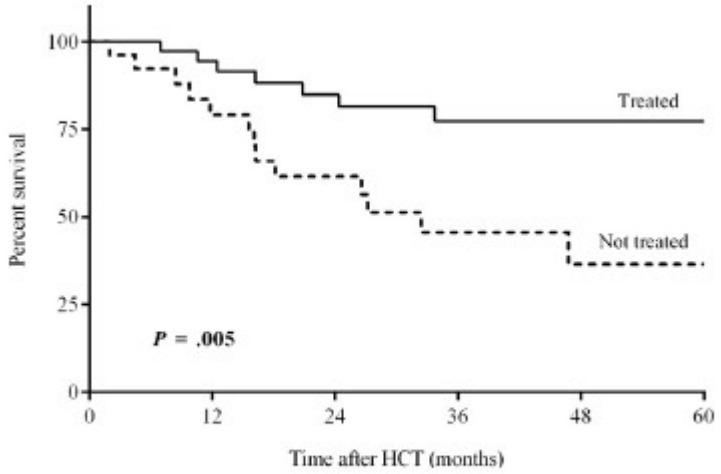
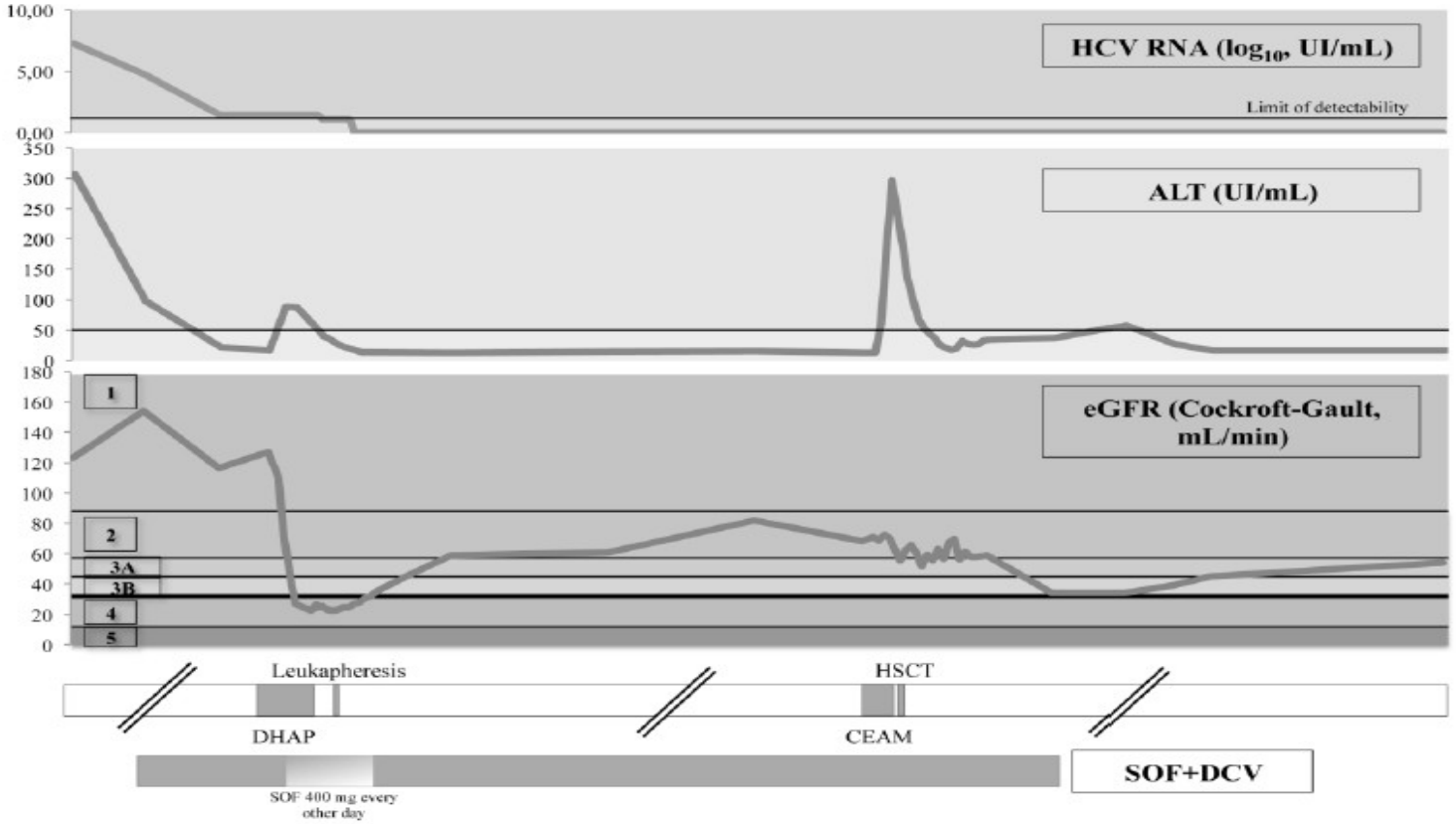



**Figure 2.** Five-year survival rates in HCV-infected cancer patients after HCT, according to the use of AVT. HCT recipients who received AVT had a significantly higher overall survival rate at 5 years (77% versus 36%; $P = .005$).

**Feasibility of all-oral anti-HCV treatment during DHAP chemotherapy and autologous stem cell transplantation for T-cell lymphoma**

Roberto Rossotti[1], Chiara Rusconi[2], Chiara Baiguera[1], Vittorio Ruggero Zilioli[2], Giovanni Grillo[2], Marco Merli[1], Emanuele Ravano[2], Massimo Puoti[1].

**Figure 1.** Virologic, alanine amino transferase (ALT) and estimated creatinine clearance (eGFR) trend over time in Patient #1.




New Microbiol 2018; 41(1)

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**Table 1.** Clinical features of hematologic patients treated with DAA so far published.

| Author | N | Histology | DAA regimen | Chemotherapy regimen | Timing of DAA | Toxicity | SVR | Complete response |
|---|---|---|---|---|---|---|---|---|
| Carrier | 5 | Marginal zone lymphoma (2) | SOF+SMV | Rituximab | During rituximab infusion | G3 asthenia | 100% (5/5) | 100% (5/5) |
| | | Marginal zone lymphoma (1) | SOF+DCV | | | No | | |
| | | DLBCL (2) | SOF+DCV | 4 R-ACVBP, 2 Methotrexate, 4 R-VP16 | After CT | G3 liver toxicity | | |
| Merli | 2 | DLBCL (1) | SOF+SMV | R-CHOP, R-mini-DHAP followed by RT | After CT, during RT | No | 100% (2/2) | 100% (2/2) |
| | | DLBCL (1) | SOF/LDV | R-CHOP | Contemporary | | | |
| Economides | 9 | Multiple myeloma (2); Myelodysplastic syndrome (2) Acute myelogenous leukemia (1) DLBCL (1) Follicular lymphoma (1) Waldenström macroglobulinemia (1) Mycosis fungoides/T cell lymphoma (1) | SOF/LDV±RBV (52%) SOF+RBV (29%) SOF+SMV (14%) SOF+DCV (5%)* | No detailed data | Contemporary | Serious adverse events: 38% (8/21): G3: Anemia Neutropenia Thrombocytopenia Fatigue Weight loss Headache G4: Abdominal pain Fatigue | 95% (20/21)* | No data |
| Kyvernitakis | 14 | Leukemia (14); Non-Hodgkin lymphoma (20); Hodgkin lymphoma (9); Multiple myeloma (25); other (1)* | SOF+RBV (6) SOF+SMV (2) SOF/LDV±RBV (6) | No detailed data | After HSCT | G3 anemia No G3 hyperbilirubinemia | 85% (11/13) | 32/64 (50%)* |
| **Total** | **30** | | | | | **29% (12/42)*** | **90% (18/20)**** | **55% (39/71)^** |

# Haematology and HSCT


## WHO SHOULD BE TREATED AND HOW?

**Statement**

1. HCV RNA positive patients with B cell NHL should be treated for HCV infection with currently approved DAA regiments (GRADE 1B).

Patients with rapidly progressive and symptomatic indolent lymphomas and those affected by DLBCL should undergo immunochemotherapy according to current guidelines for lymphoma. Antiviral treatment could be either be **concomitant (if feasible) or delayed,** to prevent evolution to cirrhosis and liver-disease related events, lymphoma relapse and toxicity related to immunochemotheraphy and HCV infection (GRADE 1C)

**Vote in favour: 97,9%**

# HCV
# allo-HSCT
# Donors

# Marrow Transplantation From Hepatitis C Virus Seropositive Donors: Transmission Rate and Clinical Course

By Margaret C. Shuhart, David Myerson, Barrett H. Childs, Joyce D. Fingeroth, James J. Perry, David S. Snyder, Catherine L. Spurgeon, Carol A. Bevan, and George B. McDonald

| | 12 HCV+ Donors | 12 HCV- Recipients | HCV RNA post-BMT | Hepatitis | Deaths |
|---|---|---|---|---|---|
| HCV RNA+ | 7 | 0 | 7 | 2 | 2 |
| HCV RNA- | 5 | 0 | 0 | 1 | 0 |

*Blood*, Vol 84, No 9 (November 1), 1994: pp 3229-3235

# Suppressive Anti-HCV Therapy for Prevention of Donor to Recipient Transmission in Stem Cell Transplantation

Sri Naveen Surapaneni, M.D., M.P.H., Parameswaran Hari, M.D., Josh Knox, P.A-C., Jack Daniel, R.N., and Kia Saeian, M.D., M.Sc.

*Divisions of Hematology & Oncology, Gastroenterology & Hepatology, Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin*

**A 48-yr-old man with acute myeloid leukemia (AML) required urgent allogeneic hematopoietic stem cell transplantation because of failed attempts to induce remission via chemotherapy. He had an HLA identical donor sister who was hepatitis C virus (HCV) RNA positive. In order to prevent HCV transmission to her brother, the donor was treated with weekly injections of pegylated interferon alfa-2b (150 $\mu$g subcutaneously every week) and daily ribavirin (1 g/day) for 5 wk at which time her qualitative polymerase chain reaction (PCR) was negative. Her stem cells were successfully grafted into the recipient. The recipient remained HCV PCR negative after transplant until death from relapsed AML.**

**(Am J Gastroenterol 2007;102:449–451)**

Commentary

# Expanding the Use of Organs From Hepatitis C-Viremic Donors: The Evidence Continues to Build

Courtenay M. Holscher, MD,[1] Christine M. Durand, MD,[2] and Niraj M. Desai, MD[1]

Transplantation ■ April 2018 ■ Volume 102 ■ Number 4

# HCV
# allo-HSCT
# Recipients

PLOS ONE

# Characteristics and risk of chronic graft-versus-host disease of liver in allogeneic hematopoietic stem cell transplant recipients

**Chien-Ting Chen[1,2☯], Chun-Yu Liu[2,3☯], Yuan-Bin Yu[1,2¤], Chia-Jen Liu[1,2‡], Liang-Tsai Hsiao[1,2‡], Jyh-Pyng Gau[1,2‡], Tzeon-Jye Chiou[2,4‡], Jing-Hwang Liu[1,2‡], Yao-Chung Liu[1,2]***

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **HBV status** | | | | | | | |
| Non-carrier | 313 | 20 | 6.4 | 1.00 (reference) | | | |
| carrier | 49 | 1 | 2.0 | 0.329 (0.044–2.449) | 0.277 | | |
| **HCV status** | | | | | | | |
| Non-carrier | 356 | 19 | 5.3 | 1.00 (reference) | | | |
| carrier | 6 | 2 | 33.3 | 6.684 (1.556–28.705) | 0.011 | 19.087 (3.931–92.672) | <0.001 |

Bone Marrow Transplantation (2016) **51,** 96–102

**www.nature.com/bmt**

**ORIGINAL ARTICLE**

# Risk factors and prognosis of hepatic acute GvHD after allogeneic hematopoietic cell transplantation

Y Arai[1], J Kanda[2], H Nakasone[2,3], T Kondo[1], N Uchida[4], T Fukuda[5], K Ohashi[6], K Kaida[7], K Iwato[8], T Eto[9], Y Kanda[2], H Nakamae[10], T Nagamura-Inoue[11], Y Morishima[12], M Hirokawa[13], Y Atsuta[14,15] and M Murata[16] on behalf of the GVHD working group of the Japan Society for Hematopoietic Cell Transplantation

| *Variables* | | | | N = 8378 | | % |
|---|---|---|---|---|---|---|
| *Variables related to pre-transplant liver condition* | | | | | | |
| HbsAg | | | | | | |
| (−) | | | | 8087 | | 96.5 |
| (+) | | | | 291 | | 3.5 |
| HCV-Ab | | | | | | |
| (−) | | | | 8254 | | 98.5 |
| (+) | | | | 124 | | 1.5 |
| *Variables related to pre-transplant liver condition* | | | | | | |
| HBsAg | | | | | | |
| (−) | 1.00 | (Reference) | | 1.00 | (Reference) | |
| (+) | 0.66 | (0.38–1.15) | 0.14 | 0.64 | (0.36–1.14) | 0.13 |
| HCV-Ab | | | | | | |
| (−) | 1.00 | (Reference) | | 1.00 | (Reference) | |
| (+) | 1.86 | (1.09–3.17) | 0.02[a] | 1.93 | (1.10–3.38) | 0.02[a] |

# Haematology and HSCT


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**Vote in favour: 97,9%**

# Conclusions

## HSCT in HBV and HCV patients

**HBV:**

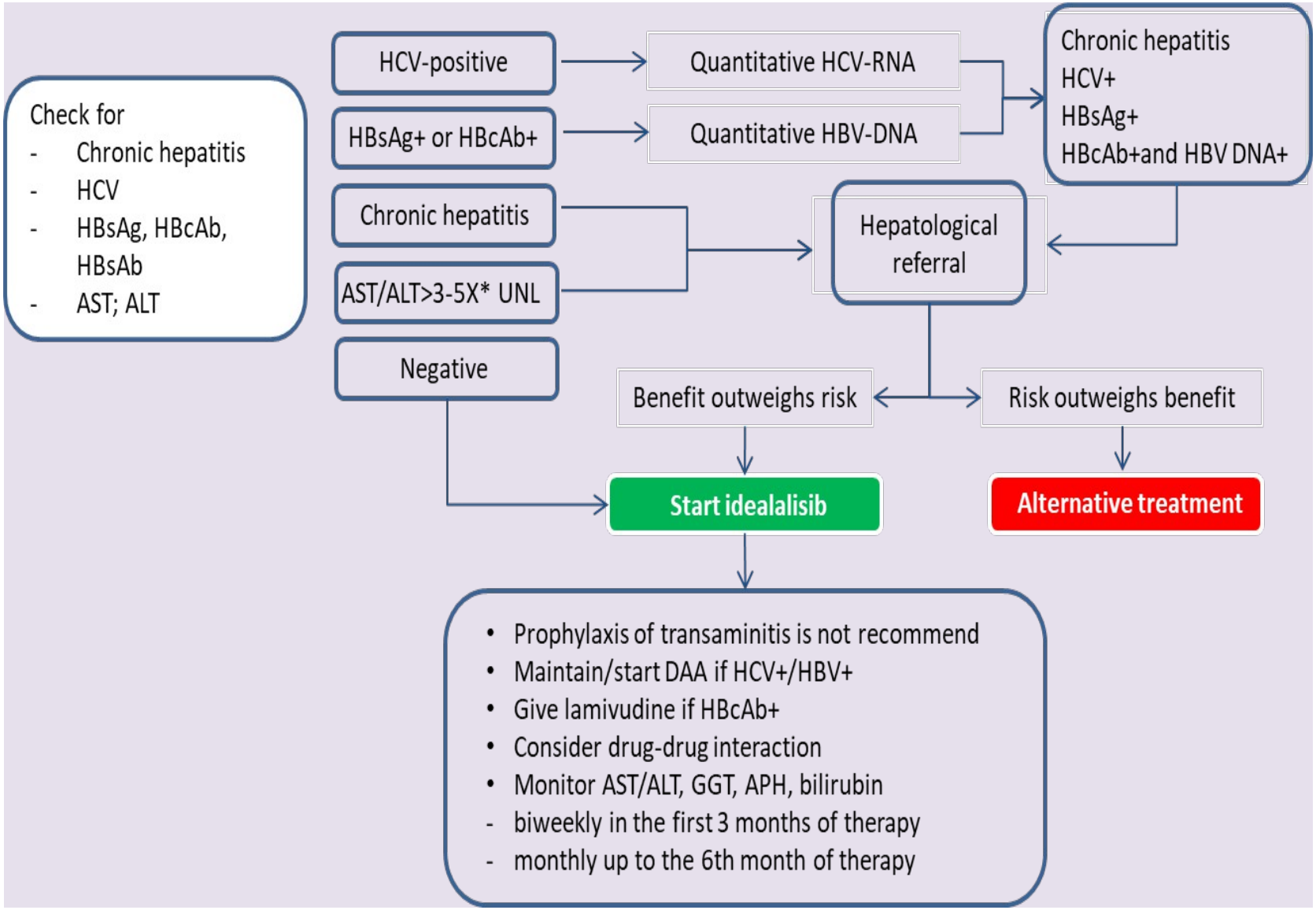
- Testing
- Treatment (DAAs): prophylaxis or therapy
- Matching in allo-HSCT
- Vaccinein some patients (allo-donors)

**HCV:**

- Testing
- Treatment (DAAs)

# Transaminitis

# Baseline


Check for
- Chronic hepatitis
- HCV
- HBsAg, HBcAb, HBsAb
- AST; ALT
HCV-positive
HBsAg+ or HBcAb+
Chronic hepatitis
AST/ALT>3-5X* UNL
Negative
Quantitative HCV-RNA
Quantitative HBV-DNA
Chronic hepatitis
HCV+
HBsAg+
HBcAb+and HBV DNA+
Hepatological referral
Benefit outweighs risk
Risk outweighs benefit
Start idealalisib
Alternative treatment
• Prophylaxis of transaminitis is not recommend
• Maintain/start DAA if HCV+/HBV+
• Give lamivudine if HBcAb+
• Consider drug-drug interaction
• Monitor AST/ALT, GGT, APH, bilirubin
- biweekly in the first 3 months of therapy
- monthly up to the 6th month of therapy

# Transaminitis