



Safety and efficacy of pegylated interferon and ribavirin in adolescents with human immunodeficiency virus and hepatitis C virus acquired perinatally

Raffaella Rosso, Antonio Di Biagio, Malgorzata Mikulska, Elena Nicco, Claudia Bernardini, Claudio Viscoli

► To cite this version:

Raffaella Rosso, Antonio Di Biagio, Malgorzata Mikulska, Elena Nicco, Claudia Bernardini, et al.. Safety and efficacy of pegylated interferon and ribavirin in adolescents with human immunodeficiency virus and hepatitis C virus acquired perinatally. *Journal of Medical Virology*, 2010, 82 (7), pp.1110. 10.1002/jmv.21802 . hal-00552414

HAL Id: hal-00552414

<https://hal.science/hal-00552414>

Submitted on 6 Jan 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Safety and efficacy of pegylated interferon and ribavirin in adolescents with human immunodeficiency virus and hepatitis C virus acquired perinatally

Journal:	<i>Journal of Medical Virology</i>
Manuscript ID:	JMV-09-1595.R3
Wiley - Manuscript type:	Research Article
Date Submitted by the Author:	11-Feb-2010
Complete List of Authors:	Rosso, Raffaella; University of Genoa, Infectious Diseases Di Biagio, Antonio; San Martino Hospital, Infectious Diseases Mikulska, Malgorzata; San Martino Hospital, Infectious Diseases Nicco, Elena; University of Genoa, Infectious Diseases Bernardini, Claudia; University of Genoa, Infectious Diseases Viscoli, Claudio; University of Genoa, Infectious Diseases
Keywords:	hepatitis C virus, ribavirin, pegylated interferon, mother-to-child transmission, human immunodeficiency virus



Table 1. Characteristics of individuals included in case series

Patient	Age	Gender	Weight (Kg)	CDC	CD4+	HIV-RNA copies/mL	Genotype	HCV VL Log ₁₀	ALT/AST	PEG IFN mcg	Ribavirin mg	ARV	Change ARV During HCV therapy	Weeks of PEG- IFN/ ribavirin	RVR	EVR	SVR
1	20	M	64	A2	329	60,000	3a	7.50 x 10 ⁵	211/135	alfa 2a 180	800	no	no	24	yes	yes	yes
2	18	F	66	B2	474	<50	3a	1.42 x 10 ⁶	220/122	alfa 2b 100	800	ABC + 3TC + LPV/rtv	no	36	yes	yes	yes
3	15	M	49	A1	585	2,600	1a	4.96 x 10 ⁵	50/44	alfa 2b 80	800	ABC + 3TC	3TC	36	no	yes	no
4	19	F	48	A2	663	10,400	3a	4.3 x 10 ⁵	37/30	alfa 2b 80	800	3TC	no	24	no	no	no
4 R	20	F	49	A2	681	<50	3a	5.19 x 10 ⁴	37/34	alfa 2a 180	800	FTC + TDF + ATV/rtv	ABC + TDF + ATV	36	yes	yes	no

CDC: Center for Diseases Control Classification for HIV/AIDS; VL: viral load; ALT: alanine aminotransferase; ARV: antiretroviral therapy; RVR: rapid virological response; EVR: early virological response; SVR: sustained virological response; ABC: abacavir; 3TC: lamivudine; LPV/r: Lopinavir/ritonavir; R: rechallenge FTC: emtricitabine; TDF: tenofovir; ATV/r: atazanavir/ritonavir

For Peer Review

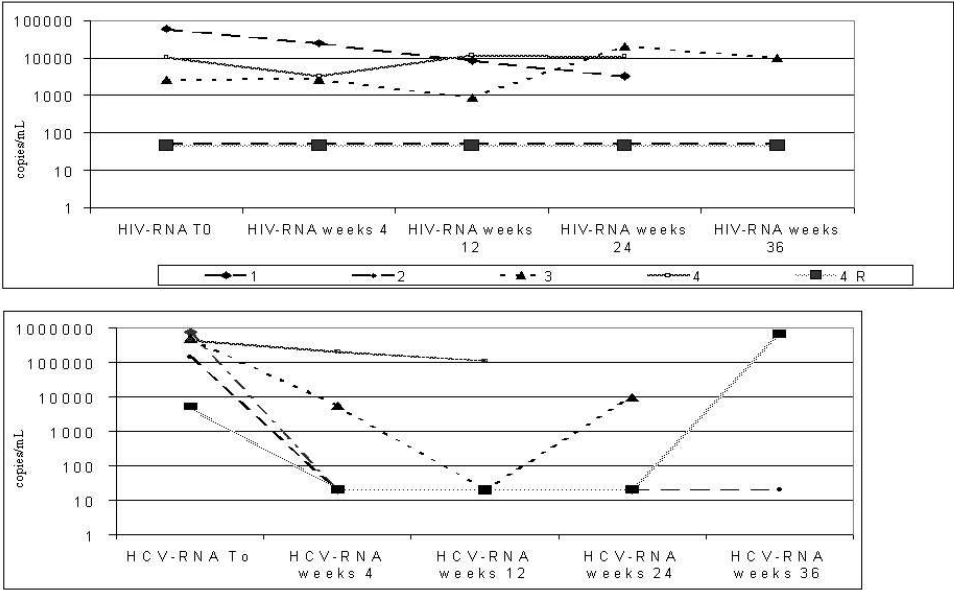


Figure 1: Depict evolution of HIV-1 RNA and HCV-RNA viral load during progression of treatment.

T0: start of PEG-IFN/ribavirin treatment

Figure 1: Depict evolution of HIV-1 RNA and HCV-RNA viral load during progression of treatment
254x190mm (96 x 96 DPI)

Safety and efficacy of pegylated interferon and ribavirin in adolescents with human immunodeficiency virus and hepatitis C virus acquired perinatally

Raffaella Rosso, Antonio Di Biagio*, Malgorzata Mikulska, Elena Nicco, Claudia Bernardini, Claudio Viscoli

Infectious Diseases Clinic, University of Genoa, San Martino Hospital, Largo R. Benzi 10, 16132, Genoa, Italy

***Corresponding author:**

Antonio Di Biagio, M.D.,
Dept. of Infectious Diseases,
San Martino Hospital, University of Genoa
Largo Rosanna Benzi 10
16132 Genova, Italy
Tel. + 39 010 5555142
Fax + 39 010 3537680
E-mail: antonio.dibiagio@hsanmartino.it

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Abstract

Limited evidence is available currently regarding the efficacy and safety of pegylated interferon and ribavirin in patients co-infected perinatally with human immunodeficiency virus (HIV) and hepatitis C virus (HCV). No information is available on whether or not these patients should be treated earlier for infection with HCV. This report describes four patients with HIV and HCV co-infection acquired perinatally, who were treated with pegylated interferon and ribavirin for chronic viral hepatitis caused by HCV.

Key words: hepatitis C virus, human immunodeficiency virus, adolescents, perinatal transmission, mother-to-child transmission, pegylated interferon, ribavirin.

Introduction

Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) share the same routes of infection, therefore, co-infection with HCV is very common in patients infected with HIV (occurring in at least 30% of cases), with significant morbidity and mortality [Alter, 2006]. HIV infection aggravates the clinical course of HCV infection and reduces the rate of sustained virological response to pegylated interferon (PEG-IFN) and ribavirin [Shire et al., 2007]. Co-infected individuals have higher HCV-RNA levels [Daar et al., 2001], and progress to cirrhosis and end-stage liver disease more rapidly than those with HCV infection alone [Benhamou et al, 1999].

Therefore, the best management of hepatitis C in adults with co-infection is still controversial. In patients who are co-infected vertically or by perinatal transmission of both viruses, the condition is even more uncertain. It is known that the prevalence of HCV in pregnant women infected with HIV ranges from 12% to 28%, with mother-to-child transmission rates ranging from 3.6% to 9.5% [England et al., 2006; Landes et al., 2008], but no guidelines are available on the most appropriate clinical management. Most patients co-infected vertically have normal hepatic function and require no treatment. Management is usually based on clinical monitoring, biochemical testing of liver function, ultrasound imaging, and sometimes, liver biopsy. However, in the light of the improved efficacy and tolerability of treatment strategies in adults, children and adolescents with vertically acquired HIV/HCV co-infection might benefit from HCV treatment.

From a treatment perspective, the current guidelines by the British HIV Association (BHIVA) on HIV/HCV co-infection in adults vary depending on the timing of the diagnosis of HIV and HCV infection [Nelson et al. 2005]. If co-infection is identified before HIV therapy is indicated, treatment for HCV should be considered to elicit a better response to HIV therapy and to limit liver damage caused by some antiretroviral drugs. If co-infection is diagnosed at a point when the patient requires or is receiving combined antiretroviral treatment (cART), delaying progression of HIV takes priority over HCV treatment [Nelson et al., 2005]. Treatment of children and adolescents co-infected with HIV and HCV is complicated further by the limited number of HIV drugs available

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

for pediatric use, thus making it more difficult to avoid drugs with liver toxicity, and by the absence of HCV treatment approved for children and adolescents [England et al., 2009]. In adults, treatment strategies have evolved from monotherapy with interferon- α (IFN- α), to combination therapy with PEG-IFN and ribavirin, which forms the basis of current recommendations. PEG-IFN is not approved at present for patients <18 years of age, even for HCV infection alone, although early studies with IFN- α monotherapy have suggested a significantly higher sustained virological response in children compared to adults (36% vs. 8%) [Jacobson et al., 2002].

PEG-IFN treatment of four adolescents with HIV and HCV infection acquired perinatally.

Case reports

The following methods were used for virological and immunological assessment: Beckman Coulter, (Fullerton, CA, USA) for CD4+ count; Versant HIV-1 RNA 3.0 assay bDNA (Siemens Medical Solutions Diagnostics, Malvern, PA, USA) for HIV-RNA level; and Cobas Ampliprep and TaqMan Roche (Molecular System Inc, Branchburg, NJ, USA) for measurement of HCV RNA.

The characteristics and outcome of the four patients described are outlined in Table 1. None of the patients had ultrasound evidence of cirrhosis.

Patient 1

A 20-year-old male Caucasian young adult with HCV (genotype 3a) and HIV-1 (clade B) infection acquired perinatally was started on PEG-IFN- α 2a 180 μ g once weekly and ribavirin 800 mg/day because of persistent elevation of liver enzymes, HCV-RNA load of 7.50×10^5 IU/mL (5.87 log), and a favorable genotype. At that point, the patient had a CD4+ cell count of 307 cells/mm³ (18%) and HIV viral load of 60,000 copies/mL, because of suboptimal cART with tenofovir and didanosine and a lack of compliance. To improve compliance, cART was stopped when HCV treatment was introduced. A rapid viral response was observed, with undetectable HCV-RNA load at weeks 4, 12 and 24 of treatment (Figure 1). At week 12 of treatment, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) reverted to normal levels (40 U/L and 26 U/L,

respectively). PEG-IFN/ribavirin were stopped at week 24, because the patient reported subcutaneous injection fatigue. No other side effect was detected throughout the treatment period. During HCV therapy, no cART was administered, because we were concerned about possible poor compliance. Nevertheless, good immunological control was maintained (CD4⁺ median value 289 cells/mm³, range 243–311 cells/mm³), with low HIV-RNA replication (median value 4,700 copies/mL, range 3,500–60,000 copies/mL). Sustained viral response for HCV was confirmed at the last follow-up visit 3 years after the end of treatment.

Patient 2

An 18-year-old female Caucasian young adult, with HCV (genotype 3a) and HIV-1 (clade B) infection acquired perinatally was considered suitable for HCV treatment because of persistently active hepatitis (ALT and AST 3–5 times above the upper limit of normal) and high HCV-RNA level (1.42×10^6 IU/mL, 6.15 log). At the beginning of HCV treatment, she presented with good immunological and virological status (CD4⁺ 474 cells/mm³, 35%, HIV RNA <50 copies/mL) as a result of an optimal response and compliance to cART based on abacavir, lamivudine and lopinavir/ritonavir. She started PEG-IFN- α 2b 100 μ g once weekly and ribavirin 800 mg/day, and had undetectable HCV-RNA levels at weeks 4, 12 and 24 and at the end of therapy (Figure 1). Additionally, liver enzymes returned to normal levels at week 24 of treatment (AST 31 U/L, ALT 24 U/L).

PEG-IFN and ribavirin were stopped after 36 weeks because of an iatrogenic defluvium capillorum (alopecia). At the follow-up visit, 24 weeks after the end of HCV treatment, HCV RNA remained undetectable. There were no other adverse events reported during treatment; the patient continued the same cART and HIV-RNA load remained undetectable.

Patient 3

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

A 15-year-old male Caucasian adolescent with vertically acquired HCV (genotype 1a) and HIV-1 (clade B) infection was started on HCV treatment with PEG-IFN- α 2b 80 μ g once weekly and ribavirin 800 mg/day because of persistently elevated levels of AST and ALT and HCV-RNA load of 4.96×10^5 IU/mL (5.7 log). At that time, the patient had a high CD4+ lymphocyte count (585 cells/mm³, 27%) and active HIV-RNA replication (2,600 RNA copies/mL). The cART regimen was based only on abacavir and lamivudine because of suboptimal compliance.

At week 4, a partial response was observed (HCV RNA 5.51×10^3 IU/mL, log 3.74). The complete early virological response at week 12 (HCV RNA undetectable) was followed by a breakthrough (HCV RNA 9.51×10^4 IU/mL, 4.97 log) at week 24. At week 36, HCV treatment was discontinued and judged as a failure because of the patient's poor compliance (Figure 1). The levels of ALT and AST remained slightly above the normal values, with median levels of 47 U/L (range 31–63 U/L) and 52 U/L (range 29–78 U/L), respectively. As a result of concern about patient compliance during HCV treatment, we prescribed monotherapy with lamivudine, with good immunological control (CD4+ median value 443 cells/mm³, range 334–585 cells/mm³) and active HIV-RNA replication (HIV-RNA median value 900 copies/mL, range <50–2,600 copies/mL) throughout the whole period of PEG-IFN/ribavirin therapy. Then, cART based on tenofovir, emtricitabine and lopinavir/ritonavir was introduced, and 12 weeks later, HIV RNA was undetectable.

At the last follow-up, 52 weeks after the end of therapy, HCV RNA was 1.02×10^6 IU/mL (6.00 log) and AST and ALT were 32 U/L and 38 U/L, respectively, with undetectable HIV RNA and CD4+ cell count of 242 cells/mm³. HCV retreatment can be considered after thorough and intense counseling, given that, as a young adult, the patient might be more responsible and compliant than as a teenager.

Patient 4

1
2
3 A 19-year-old female Caucasian young adult with HCV (genotype 3a) and HIV-1 (clade B)
4
5 infection acquired perinatally started PEG-IFN/ribavirin therapy because of persistently elevated
6
7 HCV RNA, and a favorable genotype. At that time, she had a high CD4⁺ cell count (663 cells/mm³,
8
9 36%) and active HIV-RNA replication (10,400 copies/mL) because of lack of compliance and
10
11 multiple treatment failures. HCV RNA was 4.39×10^5 IU/mL (5.87 log), and ALT and AST were
12
13 30 U/L and 37 U/L, respectively. PEG-IFN- α 2b 80 μ g once weekly and ribavirin 800 mg/day were
14
15 prescribed. However, HCV RNA remained high at weeks 4 and 12 (2.05×10^5 IU/mL, 5.31 log and
16
17 1.16×10^5 IU/mL, 5.06 log, respectively). At week 24, the treatment was stopped because of failure
18
19 (Figure 1).
20
21
22
23

24
25 At the beginning of HCV treatment, taking into account her good immunological control
26
27 and failure of previous cART (abacavir, lamivudine and efavirenz), we decided to switch to
28
29 monotherapy with lamivudine. This was continued for 28 weeks after the beginning of HCV
30
31 treatment, with good immunological control (CD4⁺ median value 483 cells/mm³, range 427–663
32
33 cells/mm³), and active HIV-RNA replication (median value 10,650 RNA copies/mL, range 3,300–
34
35 15,700 copies/mL).
36
37

38
39 Eight months after the new cART based on tenofovir, emtricitabine and ritonavir-boosted
40
41 atazanavir was started. This resulted in a good immunological/virological situation (CD4⁺ cell
42
43 count of 681 cells/mm³, HIV RNA undetectable), HCV RNA was 5.19×10^4 IU/mL (4.72 log), and
44
45 AST and ALT were 34 U/L and 37 U/L, respectively. Therefore, new treatment with PEG-IFN- α 2a
46
47 180 μ g once weekly and ribavirin 800mg/day was started. A rapid virological response was present
48
49 at week 4 and HCV RNA remained undetectable at weeks 12 and 24. However, at week 36,
50
51 virological breakthrough was detected (6.74×10^5 IU/mL, 5.82 log) and HCV treatment was
52
53 stopped (Figure 1). At the follow-up visit after 8 weeks, HCV-RNA level was high (1.23×10^6
54
55 IU/mL, 6.08 log) but AST and ALT levels were normal. No adverse effect occurred during the
56
57 PEG-IFN/ribavirin therapy.
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Three months later, the patient experienced gastrointestinal intolerance to ritonavir, which lead to poor compliance and an increase in HIV RNA. Thus, the cART was changed successfully to abacavir, lamivudine and atazanavir without ritonavir-boosted (CD4+ cell count 635 cells/mm³, HIV RNA undetectable).

Discussion

In adolescents with HIV and HCV acquired perinatally, the clinical and therapeutic approach to chronic HCV infection remains undefined. Selecting these patients for antiviral therapy is challenging given the incomplete understanding of the natural history of HCV infection in adolescents and the side effects associated with treatment. The introduction of PEG-IFN in adults has improved response rates, and it could be an attractive option in adolescents because of its weekly dosing.

To date, up to 40% of HIV/HCV co-infected adults can achieve a sustained virological response with PEG-IFN/ribavirin, and the ability to achieve such a response depends on adhering to recommended doses of both drugs and on patient compliance [Sulkowski & Benhamou, 2007]. The outcome of this combined treatment in terms of sustained virological response is known to be less favorable in HCV/HIV co-infected patients than in those infected with HCV alone [Chung et al., 2004], and seems to be associated with HCV genotype, HIV RNA and CD4+ cell count [Sulkowski, 2008], even if recent studies have suggested a non-predictive role of immunological and virological status in treatment response [Quesnel-Vallières et al., 2008].

The rates of HCV-RNA clearance are significantly higher in cART-treated than in untreated adult patients, regardless of HCV genotype [Sulkowski, 2008]. Moreover, several studies in adults have suggested that duration of infection might be more important than virus genotype in the progression of HCV-associated liver disease [Rockstroh et al., 2008].

1
2
3 In untreated children and adolescents, only few data are available, but the clearance is
4 associated independently with genotype 3 and with infection diagnosed early in life [Resti et al.,
5 2003].
6
7
8
9

10 In this limited study, adolescents with HIV and HCV acquired perinatally seem to respond
11 well to PEG-IFN and ribavirin. Indeed, patients 1 and 2 presented a rapid virological response and
12 subsequent sustained virological response. However, both patients had genotype 3 and good
13 immunological control during HCV treatment. The other two patients failed PEG-IFN and ribavirin
14 treatment, probably because of problems with compliance. Indeed, patient 3, with a less responsive
15 genotype (1b) failed HCV treatment despite an early virological response. Patient 4, with a
16 favorable genotype, initially did not respond to HCV treatment when she had high HIV-RNA
17 levels. After HIV viral load became undetectable, she responded rapidly to PEG-IFN/ribavirin
18 retreatment but eventually she failed because of poor compliance.
19
20
21
22
23
24
25
26
27
28
29
30
31

32 Although the study was limited by its small sample size and retrospective nature, in young
33 adults with vertically acquired HCV/HIV co-infection, PEG-IFN/ribavirin therapy seems to show
34 promising efficacy similar to that described in adults. No liver biopsy was performed before
35 treatment, according to the most recent guidelines for HCV management in co-infected adult
36 patients. Indeed, given the high response rate to treatment based on PEG-IFN/ribavirin, the faster
37 progression of hepatic disease in co-infected patients, and the possibility of evaluating treatment
38 response by monitoring HCV RNA, liver biopsy is no longer mandatory [Rockstroh et al., 2008].
39
40
41
42
43
44
45
46
47

48 In the setting of co-infection, the recommended length of PEG-IFN/ribavirin treatment is 48
49 weeks, regardless of genotype and response to therapy. Even though in all patients HCV treatment
50 was planned for 48 weeks, it was always stopped earlier, either because of side effects/intolerance
51 (alopecia and subcutaneous injection fatigue) or failure due to poor compliance. As far as
52 tolerability is concern, it is stressed that PEG-IFN/ribavirin generally was well tolerated and none of
53 our patients experienced leukopenia or anemia, therefore, there was no need to use erythropoietin or
54 granulocyte-stimulating factors.
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

In conclusion, HCV treatment should be standardized in subjects with vertically acquired HCV/HIV co-infection, on the basis of its efficacy and tolerability. Although our four patients had been co-infected with HIV/HCV since birth, all but one had to wait 18 years before receiving HCV treatment. Given the long history of co-infection in these patients, starting HCV treatment early might prevent the development of chronic liver failure, hepatocellular carcinoma and cirrhosis. Moreover, early treatment in children might result in a better response. The main problems in adolescent patients remain lack of compliance, mostly because of age, the burden of pills, difficult management of subcutaneous injection, possible adverse events associated with PEG-IFN/ribavirin, and the difficult socio-cultural background of these patients. Good compliance is essential to achieve a sustained virological response and appeared to be a major determinant of treatment failure in the patients described. The balance of risks and benefits in the treatment of HCV and HIV infection in adolescent patients should be assessed individually. Preparation and support throughout the treatment period, both for the patient and for his/her family are needed to improve adherence and obtain a high probability of therapeutic success.

Acknowledgements

We thank all the patients who participated in the study and the nurses who cared for these patients.

Funding Source: None.

Competing interests: None declared

References

- Alter MJ. 2006 Epidemiology of viral hepatitis and HIV co-infection. *J Hepatol* 44:S6–S9.
- Benhamou Y, Bochet M, Di Martino V, Charlotte F, Azria F, Coutellier A, Vidaud M, Bricaire F, Opolon P, Katlama C, Poynard T. 1999 Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus co-infected patients. *Hepatology* 30:1054–8
- Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE, Peters MG, Koziel MJ, Bhan AK, Alston B, Colquhoun D, Nevin T, Harb G, van der Horst C; AIDS Clinical Trials Group A5071 Study Team. 2004 Peginterferon alfa 2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *N Engl J Med* 351:451–9.
- Daar ES, Lynn H, Donfield S, Gomperts E, Hilgartner MW, Hoots WK, Chernoff D, Arkin S, Wong WY, Winkler CA. 2001; Hemophilia Growth and Development Study 2001 Relation between HIV-1 and hepatitis C viral load in patients with hemophilia. *J Acquir Immune Defic Syndr* 26:466–72
- England K, Thorne C, Newell ML. 2006 Vertically acquired pediatric coinfection with HIV and hepatitis C virus. *Lancet Infect Dis* 6:83–90.
- England K, Thorne C, Pembrey L, Newell ML. 2009 Policies and practices for the clinical management of HIV/HCV coinfecting children in Europe: an epidemiological survey. *Eur J Pediatr* 168:915–917
- Jacobson KR, Murray K, Zellos A, Schwarz KB. 2002 An analysis of published trials of interferon monotherapy in children with chronic hepatitis C. *J Pediatr Gastroenterology Nutr* 34:52–58.
- Landes M, Newell ML, Barlow P, Fiore S, Malyuta R, Martinelli P, Posokhova S, Savasi V, Semenenko I, Stelmah A, Tibaldi C, Thorne C. 2008 Hepatitis B or Hepatitis C coinfection in HIV-infected pregnant women in Europe. *HIV Med* 9, 526–34.
- Nelson M, Matthews G, Brook MG et al. 2005 BHIVA guidelines on HIV and chronic hepatitis: coinfection with HIV and hepatitis C virus infection. *HIV Med* 6:96–106

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Quesnel-Vallières M, Lemay M, Lapointe N, Martin SR, Soudeyns H. 2008 HCV quasispecies evolution during treatment with interferon alfa-2b and ribavirin in two children coinfectd with HCV and HIV-1. *J of Clin Virol* 43, 236-40.

Resti M, Jara P, Hierro L, Azzari C, Giacchino R, Zuin G, Zancan L, Pedditzi S, Bortolotti F. 2003 Clinical features and progression of perinatally acquired hepatitis c virus infection. *J Med Virol* 70, 373-7.

Rockstroh JK, Bhagani S, Benhamou Y, Bruno R, Mauss S, Peters L, Puoti M, Soriano V, Tural C, EACS Executive Committee 2008. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults. *HIV Med* 9:82-8.

Shire NJ, Welge JA, Sherman KE. 2007 Response rates to pegylated interferon and ribavirin in HCV/HIV coinfection: a research synthesis. *J Viral Hepat* 14:239-48.

Sulkowski M.S, Benhamou Y. 2007 Therapeutic issues in HIV/HCV-coinfectd patients. *J Viral Hepat* 14:371-86.

Sulkowski M.S. 2008 Viral hepatitis and HIV coinfection. *J Hepatol* 48:353-67.