Instituto de Medicina Integral Professor Fernando Figueira - IMIP

Estudo da efetividade e do impacto da terapia antirretroviral em crianças e adolescentes vivendo com o HIV no Estado de Pernambuco

Edvaldo da Silva Souza

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Doutorado IMIP 2010

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Tese apresentada à Pós-graduação em Saúde Materno Infantil do Instituto de Medicina Integral Professor Fernando Figueira (IMIP) como parte dos requisitos para obtenção do título de Doutor em Saúde Materno Infantil

Área de Concentração: Epidemiologia dos Principais Problemas de Saúde Materno Infantil

Orientadora: Profa. Dra. Ana Rodrigues Falbo

Co-orientadora: Profa. Dra. Maria Cynthia Braga

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A minha família, amigos, pacientes e colegas de trabalho, com amor e gratidão por seu carinho, compreensão, apoio e incentivo durante o período de elaboração deste trabalho.

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EPÍGRAFE

"After sleeping through a hundred million centuries we have finally opened our eyes on a sumptuous planet, sparkling with color, bountiful with life. Within decades we must close our eyes again. Isn't it a noble, an enlightened way of spending our brief time in the sun, to work at understanding the universe and how we have come to wake up in it? This is how I answer when I am asked—as I am surprisingly often— why I bother to get up in the mornings."

Richard Dawkins

1941-

RESUMO

Souza, E.S. **Estudo da efetividade e do impacto da terapia antirretroviral em crianças e adolescentes vivendo com o HIV no Estado de Pernambuco.** 2010. 103 f. Tese (Doutorado) - Pós-graduação em Saúde Materno Infantil do Instituto de Medicina Integral Professor Fernando Figueira (IMIP), Recife, 2010.

A dinâmica da replicação viral e a imunopatogênese da infecção pelo HIV-1 em crianças já está bem estabelecida. Contudo, alguns aspectos relacionados à resposta e exposição às drogas antirretrovirais entre sujeitos vivendo com o HIV-1 por longos períodos ainda precisam ser esclarecidos. O objetivo da tese foi estudar a efetividade da terapia antirretroviral em crianças e adolescentes em locais de recursos escassos e em cenário híbrido (acesso total ao tratamento numa população vivendo em local de recursos escassos), os desfechos a longo prazo em adolescentes infectados pelo HIV-1 por transmissão vertical e os desfechos e preditores numa coorte histórica de crianças e adolescentes infectados pelo HIV. Para isto, uma revisão sistemática, um estudo de corte transversal e um estudo de coorte histórico foram realizados. A taxa mediana de sobrevida em crianças infectadas pelo HIV-1 em locais de recursos escassos foi 92,2% (amplitude: 80%-100%) durante um período de acompanhamento de 20,2 meses (mediana). A idade média dos adolescentes infectados pelo HIV-1 a longo prazo estudados foi 12,5 anos, a maioria foi do sexo feminino (73,5%) com um período médio de acompanhamento de 9,0 anos. Dados clínicos e laboratoriais demonstraram que 71,4% dos adolescentes não apresentavam sinais da infecção pelo HIV, 81,6% tinham contagem de linfócitos T CD4+ dentro da variação normal e 53,1% tinha níveis indetectáveis de carga viral para o HIV. A maioria dos pacientes frequentava escola (89,8%), mas falha na escola e evasão escolar foi relatada em 51,5 e 28,6% dos sujeitos respectivamente. Ao final do acompanhamento do estudo de coorte histórico, 102 (52,3%) pacientes tinha resposta de sucesso à terapia antirretroviral com uma média de tempo de qualquer tratamento de 4,9 (DP, 2,5) anos. Após ajuste de fatores basais e associados ao tratamento, o desfecho de sucesso terapêutico foi inversamente associado com o gênero masculino (razão de odds, OR = 0.5, p = .029), associado com morar na Região Metropolitana do Recife - RMR (OR = 2.8, p = .017), e fortemente associada com pacientes/cuidadores que foram considerados aderentes pelo médico (OR =19.6, p < .001). Adicionalmente, o tempo para falha do primeiro esquema antirretroviral foi negativamente associado com gênero masculino (relative hazard, RH=0,5, p =,021) e vivendo fora da RMR (RH= 0,4, p = ,009), e associado com estágio imunológico 1 do CDC 1 (RH=2,9, p = ,003) e pacientes que foram considerados aderentes pelo julgamento do médico (RH =2,2, p = ,003). A terapia antirretroviral combinada para crianças infectadas pelo HIV-1 vivendo em locais de recursos limitados é efetiva na redução da mortalidade, no controle da replicação viral e na restauração da função imunológica dos pacientes. A maioria dos adolescentes sobreviventes a longo prazo apresenta controle clínico, imunológico e virológico e altos escores de qualidade de vida, mas com limitações no desempenho escolar. A efetividade da terapia antirretroviral e duração de resposta em local cenário híbrido está associada ao gênero, local de moradia, grau de imunodeficiência e com a adesão ao tratamento.

Palavras-chave: HIV; Síndrome de Imunodeficiência Adquirida; Terapia Antirretroviral de Alta Atividade; Criança; Adolescente.

ABSTRACT

Souza, E.S. **Study of the effectiveness and of the impact of antirretroviral therapy among children and adolescents with AIDS.** 2010. 103 f. Thesis (Doctoral - Pós-graduação em Saúde Materno Infantil do Instituto de Medicina Integral Professor Fernando Figueira (IMIP), Recife, 2010.

The dynamics of viral replication and the immunopathogenesis of HIV-1 infection in children has been well established. However, some aspects related to the response and exposure to antiretroviral drugs among HIV-1 long- living subjects still have to be clarified. The objective of the thesis was to study the effectiveness of antiretroviral therapy in children and adolescents in resource limited settings and in hybrid scenario (full access to treatment in a resource limited population), the long-term outcomes among perinatally HIV-1infected adolescents and outcomes and predictors in a historical cohort of HIV-1 infected children and adolescents. For this**,** a systematic review, a cross-sectional and a historical cohort study were done. The median rate of survival among HIV-1 infected children in resource limited settings was 92.2% (range: 80% – 100%) during a follow up period of 20.2 months (median). The mean age of the long-term HIV-1 infected studied adolescents was 12.5 years, the majority were female (73.5%) with a mean follow-up period of 9.0 years. Clinical and laboratory data showed that 71.4% of adolescents did not have any signs of HIV infection, 81.6% had a CD4+ lymphocyte count within the normal range and 53.1% had undetectable HIV viral load level. The majority of patients were attending school (89.8%) but school failure and school drop-out were reported by 51% and 28.6% of the subjects, respectively. At the end of the follow-up from the historical cohort study, 102 (52.3%) patients had successful response to antiretroviral therapy with a mean time of any treatment use of 4.9 (SD, 2,5) years. After adjustment for baseline and therapy associated factors, success treatment outcome was inversely associated with male gender (odds ratio, OR = 0.5, p = .029), associated with living in Recife Metropolitan Area - RMA (OR = 2.8, p = .017), strongly associated with patients/caregiver who were adherent by physician judgment (OR =19.6, p < .001)). Additionally, the time to failure of first antirretroviral regimen was negatively associated with male gender (relative hazard, RH=0.5, p = .021) and living out of RMA (RH= 0.4, p = .009), and associated with CDC immunological stage 1 (RH=2.9, p = .003) and patients who were adherent by physician judgment (RH =2.2, p = .003). Combination antiretroviral therapy for HIV-1infected children living in resource-limited settings is effective in reducing mortality, in control burden of HIV viral replication and leading to immune restoration in the majority of patients. The majority of long-term adolescent survivors with HIV/AIDS infection presented with clinical, immunological and virological control and high scores of quality of life, but with limitations in school performance. Antiretroviral therapy effectiveness and durable response in an hybrid scenario setting was associated with gender, living location, degree of immunodeficiency and with adherence to treatment.

Key-words: HIV; AIDS; antiretroviral therapy; children, adolescent; treatment.

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LISTA DE ABREVIATURAS E SIGLAS

ABNT	Associação Brasileira de Normas Técnicas
aids	Síndrome da imunodeficiência adquirida
AIDS	Acquired Immunodeficiency Syndrome
ARV	Antirretroviral
CDC	Centers for Disease Control and Prevention
DST	Doença Sexualmente Transmissível
e.g.	exempli gratia (latim)/por exemplo
HAART	Highly Active Antiretroviral Therapy
HIC-IMIP	IMIP´s Hospital HIV Infection Clinic
HIV-1	Human Immunodeficiency Virus type 1/Vírus da Imunodeficiência Humana tipo 1
HSH	Homens que fazem sexo com homens
i.e.	id est (latim)/isto é
IF	Inibidor de Fusão
II	Inibidor da Integrase
ITRN	Inibidor da Transcriptase Reversa análogo de Nucleosídeos
ITRNN	Inibidor da Transcriptase Reversa Não-análogo de Nucleosídeos
IP	Inibidor de Protease

IMIP	Instituto de Medicina Integral Professor Fernando Figueira
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PENTA	Paediatric European Network for Treatment of AIDS
PI	Protease Inhibitor
PN-DST/Aids	Programa Nacional de Doenças Sexualmente Transmissíveis e Aids
QOL	Quality of Life.
RMA	Recife Metropolitan Area/Região Metropolitana do Recife
RENAGENO	Rede Nacional de Genotipagem
SAE-HD	Serviço de Assistência Especializada e Hospital-Dia
TARVC	Terapia Antirretroviral Combinada
TV	Transmissão Vertical
ZDV	Zidovudine

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1. APRESENTAÇÃO

1. Apresentação

Muito progresso ocorreu no manejo e tratamento da infecção pelo HIV desde o reconhecimento da aids na década de 80, quando era considerada uma doença com alta letalidade e com manejo exclusivo para o diagnóstico precoce e tratamento de infecções oportunistas[1]. Na primeira metade da década de 90, com o desenvolvimento das primeiras drogas antirretrovirais, ocorre melhora na qualidade de vida das pessoas acometidas, mas a letalidade da doença permaneceu inalterada. Até o advento do uso de terapia antirretroviral combinada (TARVC), denominada também como HAART (Highly Active Antiretroviral Therapy) a partir de 1996[2]. A combinação de pelo menos três drogas antirretrovirais de duas classes diferentes propiciou a supressão da replicação viral, restauração da imunidade e controle da aids, tornando a sobrevida dependente da estrita aderência ao tratamento e da manutenção do controle da replicação viral[3].

O autor participou do diagnóstico e acompanhamento do primeiro caso de aids de transmissão vertical no estado de Pernambuco em 1987, realizado no Instituto de Medicina Integral Professor Fernando Figueira-IMIP[4]. Em 1988, iniciou colaboração como consultor do Programa Nacional de DST/Aids (PN-DST/Aids) do Ministério da Saúde quando participou da primeira definição de caso aids em crianças no Brasil e o IMIP se tornou referência estadual para infecção pelo HIV na infância. A partir de 1992, o autor colabora com o PN-DST/Aids como consultor também para o manejo de aids pediátrica no Brasil e o IMIP se torna Centro de Referência Nacional para AIDS em crianças, treinando e capacitando profissionais de saúde de diversas regiões do país. Atualmente, o autor é consultor em quatro áreas: manejo e tratamento de crianças e adolescentes, prevenção da transmissão vertical do HIV, resistência viral (RENAGENO) e epidemiologia (definição de casos)[5,6].

Os estudos de eficácia e segurança de novas drogas são realizados primeiro em adultos e posteriormente em crianças e adolescentes. Em relação às drogas para controle da infecção pelo HIV, não foi diferente. A idéia inicial, de acordo com as evidências científicas disponíveis, era que os adultos tinham melhor resposta ao tratamento com uma combinação de drogas antirretrovirais que as crianças. Inicialmente havia a preocupação de que o uso de TARVC em locais de recursos escassos, devido ao potencial risco de falha terapêutica, poderia propiciar surgimento de cepas virais

resistentes ao tratamento[7]. A falta de consenso sobre a eficácia da TARVC em crianças e adolescentes quando comparada aos adultos era evidente no guia brasileiro de manejo da infecção pelo HIV em crianças e adolescentes e também em outros guias de tratamento internacionais, *e.g.* o americano e europeu. Tudo isto acrescido da ausência de revisões sistemáticas sobre o tema[8-10].

Foi este cenário que levou o autor a estudar a efetividade da TARVC em crianças e adolescentes, comparando-a tanto com estudos em população adulta, como em estudos realizados em locais de recursos escassos e em cenário híbrido (acesso a medicação e exames de alta complexidade em população com recursos escassos). Além de se estudar a efetividade da TARVC, identificou-se também como importante avaliar o impacto da terapia antirretroviral a longo prazo na qualidade de vida e os aspectos psicossociais dos pacientes, a da durabilidade do sucesso terapêutico a longo prazo e possíveis fatores preditores de sucesso ou falha terapêutica em crianças e adolescentes.

A apresentação desta tese de doutorado foi feita em formato alternativo, *i.e.* apresentação de artigos submetidos à publicação ou publicados como corpo de trabalho[11].

2. INTRODUÇÃO

2. Introdução

Na década de 80, com o relato dos primeiros casos de aids em homens que faziam sexo com homens (HSH) [12-13], logo se seguiram registros de casos em usuários de drogas injetáveis[14,15], em parceiras sexuais de homens com aids[16], e em hemofílicos e receptores de derivados sanguíneos[17,18]. Os primeiros casos de aids em crianças por transmissão sangüínea ou vertical no mundo[19,20] , no Brasil[21] e em Pernambuco[4] foram descritos em 1983, 1985 e 1987 respectivamente, e geralmente ocorreram dois anos após a identificação dos primeiros casos em adultos em cada localidade.

No Brasil, o Programa Nacional de DST/Aids registrou até junho de 2005 (1980-2005) 371.827 casos de aids, desses 38.837 (10,4%) casos foram procedentes da Região Nordeste, e 9.067 (2,4%) procedentes do Estado de Pernambuco. A incidência (taxa por 100.000 hab.) no Brasil (1994-2004) foi de 17, 2, enquanto que na Região Nordeste, a incidência foi de 8,7 e em Pernambuco de 8,9[21]. Em relação aos casos de aids em menores de 13 anos de idade, o Brasil registra um total de 11.901 casos, sendo 9.965 (83,7%) por transmissão vertical do HIV; em Pernambuco são registrados 264 casos de aids em menores de 13 anos de idade e 139 entre 10 e 19 anos de idade (4 casos por transmissão vertical)[i].

No início, a aids pediátrica se caracterizava por uma evolução fulminante na quase totalidade dos casos[22]. Em 1986, evidenciava-se uma melhor qualidade de vida e menor morbidade e mortalidade com o advento do uso de gamaglobulina endovenosa e tratamento de infecções oportunistas[23]. A partir de 1991, com a disponibilização do uso das primeiras drogas antirretrovirais, a aids passou a ser considerada como uma doença crônica da infância, com períodos de progressão e estabilidade[24,25]. Muitos avanços ocorreram na última década no manuseio e controle da infecção pelo HIV/aids em crianças e adultos. Esses avanços ocorreram em diversas áreas de conhecimento científico, destacando-se: história natural da infecção pelo HIV/aids[26,27]; fisiopatogenia da infecção pelo HIV/aids[28,29]; técnicas laboratoriais para diagnóstico[30-31], estadiamento e monitorização do tratamento[32,33]; diagnóstico de infecções e afecções oportunistas[34,35]; desenvolvimento de drogas antirretrovirais[37-39] e contra infecções oportunistas[40-41]. A partir de 1996, o uso da terapia antirretroviral combinada (TARVC) modificou

[i] Dados da Coordenação Estadual de DST/Aids da Secretaria de Saúde do Estado de Pernambuco - 2006.

totalmente a evolução e prognóstico dos indivíduos com infecção pelo HIV/aids, tornando a aids uma doença crônica passível de controle medicamentoso, apesar da impossibilidade de erradicação do vírus e de suspensão de tratamento até o momento atual[43,44].

O uso da TARVC, a partir de 1996, proporcionou uma diminuição marcante da mortalidade e uma maior sobrevida de duração indefinida[45]. No Brasil, o aumento do tempo de sobrevida foi bem demonstrado pelo estudo de Matida e Marcopito, que demonstrou incremento maior de sobrevida quando o diagnóstico de aids foi após o ano de 1995 (Figura 1). Por outro lado, a TARVC trouxe um novo aspecto a ser considerado principalmente para crianças e adolescentes sob tratamento, a ocorrência de efeitos adversos a longo prazo, *i.e*. dislipidemia, lipodistrofia e síndrome metabólica[46,47].

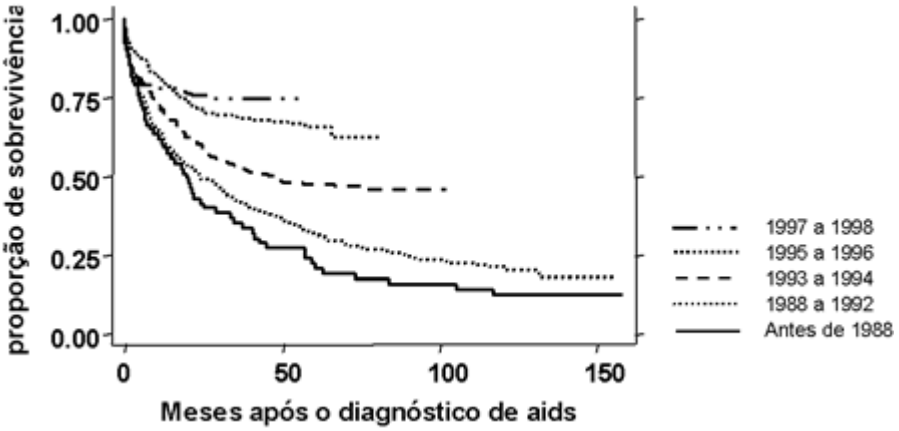

Figura 1 - Tempo de sobrevida (em meses) após o diagnóstico, de acordo com o ano do diagnóstico, em 1147 casos da amostra do estudo sobre aids-doença em crianças de 0-12 anos de idade até 31/12/1998.

Fonte: Matida LH, Marcopito LF e Grupo Brasileiro de Estudo da Sobrevida em Crianças com aids. Aumento do tempo de sobrevida das crianças com aids – Brasil. Ministério da Saúde. Boletim Epidemiológico DST/Aids Outubro de 2001 a março de 2002.

A maioria dos estudos de eficácia e ensaios clínicos com TARVC é realizada em adultos, sendo poucos os realizados em população pediátrica. Este fato traz preocupação para os profissionais de saúde quanto à eficácia de drogas antirretrovirais

em crianças e tem se refletido nos diferentes guias para crianças e adolescentes no mundo [48-53]. Os guias de manejo de infecção pelo HIV para adultos na sua maioria concordam com os objetivos do início da TARVC particularmente quanto aos parâmetros de sucesso e falha terapêutica tanto virológico quanto imunológico, diferentemente dos guias para crianças[48-52]. O guia PENTA enfatizava que uma definição de falha virológica em crianças ainda não era determinada, porém seus colaboradores concordavam que deveriam perseguir os objetivos do tratamento antirretroviral dos adultos, *i.e.* objetivo principal de reduzir a carga viral a níveis não detectáveis pelas técnicas convencionais com esquema terapêutico potente e duradouro[10]. Os guias brasileiro e espanhol indicavam que, geralmente, não era possível se obter supressão viral na maioria das crianças e, consequentemente, o sucesso ou falha no tratamento não poderia se fundamentar nos parâmetros virológicos de supressão viral [8,53]. O guia americano enfatizava que a resposta virológica inicial em crianças poderia ser mais longa do que a dos adultos e que a supressão viral era conseguida menos frequentemente[9]. Contudo, publicação ainda em 2006, já levantava dúvidas sobre o assunto e demonstrava que a TARVC era capaz de suprimir a replicação viral em crianças com uma taxa de queda de 2.1 dias semelhante a taxa de adultos e independente da carga viral basal[54].

Diante deste panorama, identificou-se como objeto de pesquisa estudar a efetividade e impacto da TARVC em crianças e adolescentes vivendo com aids acompanhados no Serviço de Assistência Especializada – Hospital-Dia (SAE-HD) do IMIP. O SAE-HD foi criado em 2003e oferece assistência multiprofissional a crianças, adolescentes, gestantes e adultos com infecção pelo HIV/Aids.

De 1987 a dezembro de 2005, o SAE-HD do IMIP registrava 302 casos de aids em menores de 13 anos de idade. Deste total, 227 (75,1%) estão vivos e em acompanhamento no SAE-HD. Foram registrados 54 (17,9%) óbitos, 15 (5%) de perdas de seguimento e 6 (2%) casos de transferência para outros serviços (TABELA 1).

Sendo 56 casos acompanhados na faixa etária de 10 a 19 anos, 55 (98,3%) casos por transmissão vertical, e apenas um caso por transmissão sangüínea ainda no primeiro

ano de vida[ii]. Quando se observou que a distribuição de casos de acordo com faixa etária atual em acompanhamento estava mudando, que o maior número de casos estava agrupado na faixa etária de 5 a 9 anos de idade, provavelmente devido a prevenção da transmissão vertical (TV) do HIV e diminuição de casos em menores de 5 anos de idade. Adicionalmente, podemos antever uma tendência à inversão da base da pirâmide com o aumento de sobrevida e envelhecimento de grupos etários mais jovens (FIGURA 2).

Desde o diagnóstico do primeiro caso de aids pediátrica no Estado de Pernambuco, o Serviço de Assistência Especializada e Hospital-Dia (SAE-HD) do IMIP vem acumulando uma série histórica de pacientes. Está série apresenta características em seu seguimento que merecem ser destacadas. Primeiro, o acompanhamento dos pacientes sempre foi realizado pelos mesmos médicos desde 1987, inclusive durante internamentos hospitalares. Segundo, o acesso regular a realização de exames de maior complexidade e uso de TARVC (pelo menos 3 drogas) ocorreram simultaneamente desde 1997, e.g. contagem de linfócitos T CD4+ e quantificação de RNA viral (carga viral). Por último, até recentemente, o SAE-HD do IMIP era o único serviço de referência para infecção pelo HIV/aids no Estado de Pernambuco para crianças e adolescentes. Com isto, temos uma série histórica de 20 anos de acompanhamento desse grupo populacional com infecção pelo HIV/aids e 10 anos de uso de TARVC.

[ii] Fonte: Relatório interno do SAE-HD/IMIP, 2006.

Tabela 1. Distribuição de casos de aids acompanhados no SAE-HD do IMIP (1987-2005) segundo a faixa etária e situação em dezembro de 2005.

Faixa Etária (em anos)	Vivos	Óbitos	Perdas	Transf.	Total
	N (%)	N (%)	N (%)	N (%)	N (%)
0 - 4	62 (80)	9 (11,5)	5 (6,4)	2 (2,6)	78 (100)
5 - 9	109 (87,2)	11 (8,8)	3 (2,4)	2 (1,6)	125 (100)
10-14	44 (73,3)	13 (21,7)	2 (3,3)	1 (1,7)	60 (100)
15-19	12 (52,2)	9 (39,1)	2 (8,7)	0	23 (100)
≥ 20	0	12 (75)	3 (18,8)	1 (6,2)	16 (100)
Total	227 (75,1)	54 (17,9)	15 (5)	6 (2)	302 (100)

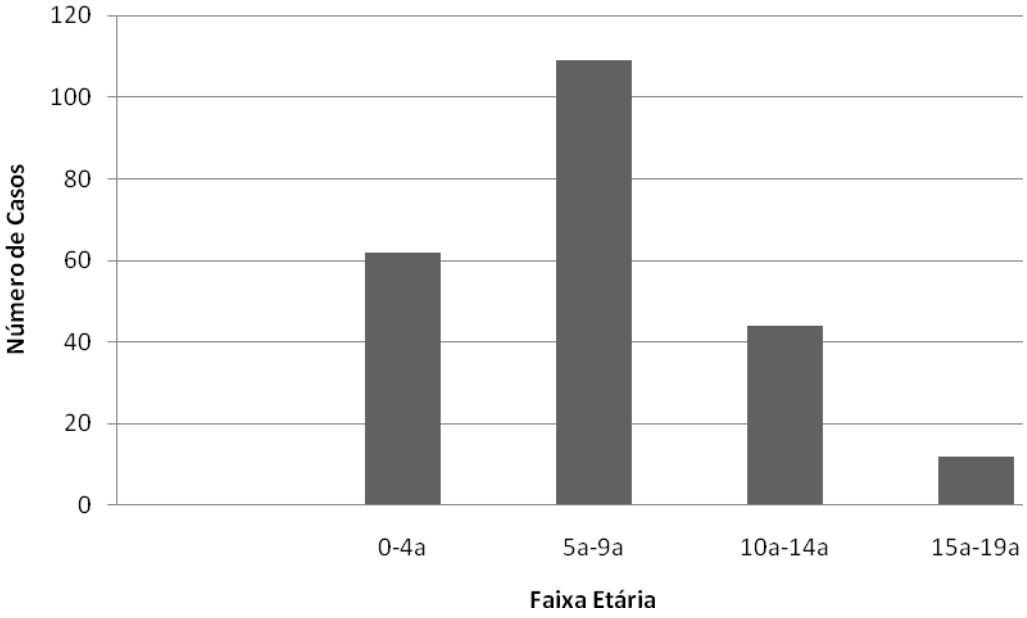

Figura 2: Distribuição de casos de aids em acompanhamento no SAE-HD do IMIP de acordo com faixa etária em dezembro de 2005 (1987-2005).

3. DESENVOLVIMENTO

3. Desenvolvimento

Estado da arte da terapia antirretroviral em crianças

O estado da arte sobre a terapia antirretroviral em crianças e adolescentes no Brasil está compilado na publicação do PN-DST/Aids intitulada "Recomendações para Terapia Antirretroviral em Crianças e Adolescentes Infectados pelo HIV", que orienta o tratamento da infecção pelo HIV, estando tanto o acesso aos exames de alta complexidade, como a dispensação e liberação dos medicamentos atrelada às suas recomendações. Este guia é atualizado periodicamente pelo Comitê Técnico Assessor para Terapias Antirretroviral e Profilaxia para Crianças e Adolescentes do PN-DST/Aids, da Secretaria de Vigilância em Saúde do Ministério da Saúde. As mudanças são feitas tendo em base as mais atuais evidências científicas e as recomendações recebem gradação de acordo com os níveis de evidências. O autor faz parte deste Comitê desde 1992 e participou na redação, revisão técnica e divulgação da última revisão publicada em 2009[53].

A terapia antirretroviral combinada tem como objetivo reduzir a morbimortalidade, assegurar crescimento e desenvolvimento, restaurar ou manter o funcionamento adequado do sistema imunológico. Isto tudo é conseguido através da supressão máxima e continuada da replicação viral. A TARVC está indicada para todas as crianças abaixo de um ano de idade assim que confirmada a infecção pelo HIV, independentemente de sintomatologia, contagem de linfócitos T CD4+ e carga viral do HIV. Nos maiores de um ano de idade, a indicação vai depender do grau de sintomas, imunodepressão e amplitude da carga viral[53].

Atualmente existem cinco classes de drogas antirretrovirais liberadas para uso na infância e adolescência: inibidor da transcriptase reversa análogo de nucleosídeos (ITRN), inibidor da trasncriptase reversa não-análogo de nucleosídeos (ITRNN), inibidor de protease (IP), inibidore de efusão (IF) e inibidor da integrase (II). A TARVC no seu esquema inicial para os pacientes virgens de tratamento deve conter três

drogas antirretrovirais de duas classes diferentes. O esquema preferencial de drogas antirretrovirais inicial deve conter duas drogas ITRN + um ITRNN ou um IP[53].

A resposta terapêutica é considerada como efetiva quando se consegue um queda de mais de 1,0 $\log_{10}$ na carga viral após 8-12 semanas de tratamento e indetecção continuada após 6 meses de tratamento. Por outro lado, considera-se falha terapêutica quando ocorre rebote da replicação viral após indetecção. Entre os vários fatores que podem influenciar o tipo de resposta terapêutica em crianças e adolescentes, destaca-se a adesão estrita ao tratamento e a dependência de terceiros (cuidadores)[53].

Problemas de pesquisa

As perguntas de pesquisa identificadas de acordo com o cenário (relevantes) e requerendo respostas (conteúdo inovador) foram:

- A efetividade da TARVC medida pela supressão viral é diferente em crianças vivendo em locais com recursos escassos?
- Qual é a efetividade e o impacto da TARVC em adolescentes com infecção pelo HIV de aquisição vertical na qualidade de vida e nos aspectos psicossociais a longo prazo?
- Qual a efetividade da TARVC e quais fatores preditores de sucesso em crianças e adolescentes com infecção pelo HIV em um cenário híbrido, livre acesso a medicamentos e exames numa população carente de recursos?

Resolução dos problemas

Para responder estas questões, o autor realizou uma revisão sistemática (publicada eletronicamente,, um estudo de corte transversal (publicado) e um de coorte histórico (submetido e sendo avaliado por pareceristas), além de uma carta ao editor (APÊNDICE 1) e revisão sistemática (APÊNDICE 2) como parte de disciplinas do curso de doutorado em Saúde Materno Infantil. Os produtos desta tese serão apresentados na seguinte ordem:

1. Primeiro Artigo: Revisão sistemática com o objetivo de determinar a taxa de sobrevida em crianças com aids usando TARVC em países com recursos escassos. Essa revisão sistemática originou o artigo intitulado "What is the effectiveness of highly active antiretroviral therapy among children HIV-infected living in resources-limited settings?", submetido e publicado em versão eletrônica no sítio da International Child Health Review Collaboration (disponível em http://www.ichrc.org).

2. Segundo Artigo: Estudo de corte transversal com o objetivo de descrever as características sociodemográficas, clínicas, laboratoriais e qualidade de vida de adolescentes infectados pelo HIV por transmissão vertical. O estudo originou artigo intitulado "Long-term Follow-up Outcomes of Perinatally HIV-infected Adolescents: Infection Control but School Failure", submetido e publicado em 2010 no Journal of Tropical Pediatrics.

3. Terceiro Artigo: Estudo de coorte histórico com o objetivo de avaliar a resposta ao uso de antirretrovirais (efetividade e durabilidade) e de identificar fatores preditores do tipo de resposta. O estudo originou um artigo intitulado "Predictors of long-term antiretroviral therapy effectiveness among HIV-1 infected children in a hybrid scenario: does gender matter?", submetido (ANEXO 1) ao Pediatric Infectious Diseases Journal em 1º de fevereiro de 2010 e em etapa de avaliação.

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5. PRIMEIRO ARTIGO

International Child Health Review Collaboration

What is the effectiveness of highly active antiretroviral therapy among children HIV-infected living in resources-limited settings?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at: http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *What is the effectiveness of highly active antiretroviral therapy among children HIV-infected living in resources-limited settings?*

Introduction:

The UNAIDS ´´AIDS epidemic update 2008`` estimated that globally the numbers of children living with HIV increased from 1.5 million in 2001 to 2.5 million in 2007. However, estimated new infections among children declined from 460,000 in 2001 to 430,000 in 2007. Deaths due to AIDS among children has increased from 330,000 in 2001 to 360,000 in 2005, but have now begun to decline to an estimated 330,000 in 2007. Sub-Saharan Africa remains the most affected region in the global AIDS epidemic. More than two out of three (68%) adults and nearly 90% of children infected with HIV live in this region, and more than three quarters (76%) AIDS deaths in 2007 occurred there [1].

Most of the studies and clinical trials on the efficacy of highly active antiretroviral therapy (HAART) have been conducted in adult populations. Although the clinical efficacy of HAART in children and adolescents has been well documented in industrialized countries, there are few data from the resource-limited settings (RLS), in which it is estimated that less than 5% of HIV-positive children have access to HAART.[2]

Important obstacles to scaling up HAART in children living in RLS include: (a) lack of human capacity and limited training and experience in treating children; (b) lack of practicable, acceptable and available paediatric antiretroviral formulation; (c) no fixed-dose combination, nor practicable paediatric antiretroviral formulation (d) high cost of paediatric antiretroviral medications; and (e) lack of affordable and simple HIV-diagnostic testing technologies for children under 18 months of age [3, 4].

The aim of this systematic review was to summarize the evidence available for effectiveness of combination antiretroviral therapy for HIV-infected children living in resource-limited settings. The primary objective of this review was to determine the rate of survival of among children using HAART. The secondary objectives were to assess the rate of viral suppression and to evaluate the immune restoration by the increase of CD4 absolute cells count or percentage. We also describe some features of the study groups such as age, baseline CD4 count and viral load, prior use of ARV drugs and nutritional status.

Methodology

Initially, we searched the Cochrane Reviews for systematic reviews on HAART among children in RLS but there were no reviews. We further used PubMed as reference to perform this review followed by search in others Electronic Databases.
Criteria for considering studies for this review

Types of studies

All experimental, quasi-experimental and observational studies using antiretroviral therapy

for HIV-1-infected children in RLC were included.

Types of participants

Studies comprising infants, children and adolescents HIV infected from birth to 18 years of age were evaluated. We included studies with all-age children infected by mother-to-child transmission and other routes (sex or blood). Studies including adult HIV infected were excluded.

Types of interventions

The intervention required was the use of antiretroviral therapy including at least 3 drugs from two or three classes of the antiretroviral drugs (NRTIs, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors and PI, protease inhibitors).

Types of outcome measures

The first outcome measured was the survival of HIV-infected children, as the proportion of alive children at the end of the follow up (in weeks).

The second outcome measured was the proportion of children with HIV RNA viral load below of detection level. There are different levels of detectability threshold depending on the type of the assay used. For analysis we allocate the levels on two groups ($\leq$ 500/400 copies/ml or $\leq$ 50/40 copies/ml) over time (weeks of follow-up).

The third measured outcome was the absolute T CD4+ lymphocyte cells count or percentage increase compared with the baseline values.

Search strategy for identification of studies

Firstly, an electronic search was made in distinct databases (see below). Secondly, the reference sections of identified papers were examined for additional publications. Finally, for every study we made a summary table to assist reviewers' analysis and evaluation.

Electronic searches

Electronic Databases used in the search strategy were: Cochrane Library, PubMed and SCIELO. First, we searched for: "HAART or highly active antiretroviral therapy", "efficacy or effectiveness", "HIV-infected child or children´´, ´´pediatric or paediatric" and "developing countries or resource-limited settings". In addition, we limited the search by age group, considering all children (0 < 18 years) and type of article: clinical trial, review, randomized controlled trial. The search was not limited by language and was done until May 31, 2008.

Other Sources

The primary search was supplemented with an exploration in AIDSSEARCH and AIDSINFO with the aim to identify other reference lists.

1. *Selection of Studies*

All titles and abstracts that included clinical trials or observational studies were retrieved if the main outcome variable was the rate of survival or the viral suppression rate under HAART (using either viral load $\leq$ 500/400 copies/ml or $\leq$ 50/40 copies/ml). To study immune restoration scope, we included studies with the increase of CD4 cells count or percentage from baseline value. The citations identified had their full text articles selected for potential inclusion.

2. *Data extraction, data management and assessment of methodological quality of included studies*

The data extraction was resumed in a table composed for every study using the PICO analysis (clearly structured question constructed to search for evidence in the literature). Prospective observational studies were assessed by detailed description of the study design and the experimental studies were assessed by using the CONSORT (Consolidated Standards of Reporting Trials). Study quality was completed by two independently reviewers (ES and CM).
We created a table containing the authors' identification of the citations retrieved, number of participants, median age, follow up period and measurement of viral load detectability threshold, baseline CD4 count, type of HAART combination, viral load level of detection, the year of publication and type of study design. Two reviewers independently evaluated the methodological quality of studies, disagreements were resolved by discussion of criteria when required. The studies were scrutinized for methodological quality, bias, internal and external validity.

3. *Measures of survival rate, viral suppression rate and immune restoration*

The measures of survival was the proportion of children alive at the end of the follow up. The measure viral suppression rate achieved after HAART was the proportion of patients with detectable level under either ≤ 500/400 or ≤ 50/40 copies/l. The measure of CD4+ lymphocytes cells count or percentage increase was the difference between baseline and end-point values.

4. *Unit of analysis issues*

Some studies had multiple treatment groups. We only extracted and included data of the treatment groups using HAART with 3 or more classes of drugs: 2 nucleoside reverse transcriptase inhibitors (NRTIs) + non nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitor (PI).

5. *Dealing with missing data*

Some of the selected studies had not all the outcome measures included in this review. Some of them had the rate of survival but not the viral suppression, other had CD4+ lymphocyte cells count and not percentage. However, all studies were included for subgroup analysis. Studies with missing descriptive and analytical statistics were excluded.

6. *Data synthesis*

Statistical analysis was performed using version 9.2 of STATA software. The Chi-square test or Fisher exact test was used to compare categorical data. Logistic regression analysis was used to determine if the duration on follow-up were associated with survival rate. A *p-value* of < 0.05 was regarded as statistically significant.

Results

The initial broad search yielded a total of 1808 references, but only 334 met the inclusion broad criteria. This number was reduced to 151 (refined criteria) and after quality control procedure to 18. Reasons for study exclusion included: some studies used data from earlier publications on the same participants, used only on-treatment analysis and do not have rate of survival viral or load threshold as an outcome variable. A summary of the characteristics of all included studies is showed at Table 1 [3, 5-21].

Thirteen out of 18 (72%) studies had survival as primary outcome. Additionally, fourteen out of 18 (78%) studies had viral suppression rate as second outcome with different threshold level of viral detectability assays. All of studies, except one (94.4%), had as secondary outcome the increase of CD4+ lymphocyte cells count or percentage.

Description of the studies:

1. Included Studies

The included studies had the follow profiles:

Study design and publication year: from the 18 papers included, 11 (61.1%) papers were retrospective observational studies, 7 (38.9%) were prospective studies; 3 out of 18 (16.6%) were experimental studies. Eleven (61.1%) out of 18 studies were published at 2007.

Patient population: a total number of patients included in all studies was 8,519 (median 473 patients/study, range: 26- 4,875). The median age when starting HAART was 85 months (range: 23 – 156 months).

At baseline, in 12 out of 18 studies, median viral load was 5.34 $\log_{10}$ copies/ml (range: 4.84 – 6.1) and in 13 out of 18 studies, patients median CD4 percentage was 9% (range: 3.5% - 20.1%), while in 12 out of 18 studies, CD4 count was 239.5 (range: 46 – 584).

Interventions: Highly Active Antiretroviral Treatment (HAART) consisted of 3 drugs of 2 or 3 classes: 2 NRTIs + NNRTI (61%) or PI (11%), NNRTI+PI (28%). The median follow-up period was 20.2 months (range: 6 - 48). According to a pre-exposure to antiretroviral drugs: 11 (61.1%) studies had included only naïve patients and 7 (38.9%) studies had both naïve and ARV experienced patients.

Outcomes: the median rate of survival was 92.2% (range: 80% – 100%) during a median follow up period of 20.2 months. No significant difference was observed in term of mortality between children receiving a NNTRI-based regiment and those receiving a PI-based regiment ($p = 0.917$).

To demonstrate virological decay, the majority of the studies (8/13) used the percentage of decrease of copies/ml, while others studies used percentage of individual under the lower level of detection assay. The studies that had as outcome viral load suppression (14/18), all demonstrated a statistical significant decrease on percentage of plasma HIV-1 RNA load. However, only 7 studies used the lower limit of assays detection as outcome, 4/18 (11.1%) studies used a limit of 400 copies/ml assays showed mean rate of viral suppression of 61.5 (37.9 to 81.0) and 3/18 (16.6%) studies used a limit of 50 copies/ml assay showed mean rate of viral suppression of 73,7 (67.7 to 83.3).

In regard to immune restoration, data described in the studies differed in many ways. Of the 17 studies that displayed median CD4 cell count or percentage, all of them demonstrated statistical significant increase compared with baseline values, but according to the increase of percentage of CD4 cells, only 2 (11.1%) studies used setpoint above 25% as absence of immunodeficiency, while the median increase of the CD4 cells count, calculated for 7 studies, was 445.3 (range: 329 – 699.8).

2. Excluded Studies

The characteristics of the excluded studies were: missing statistics and failure to measure the primary and secondary outcomes, i.e. survival or viral suppression.

Discussion

Most studies were published in 2007 (61,1%) and included a substantial number of individuals (8,519 patients). The median age of starting HAART was 7 years and did not differ when compared with other studies. [22,23] Patients baseline immunological and virological characteristics before starting HAART are according with WHO and international guidelines, *i.e.* evidence of immunodeficiency (median CD4 + cell percentage and absolute count) and viral load > 100.000 copies of HIV-RNA/ml. [24-27] The elevated median rate of survival (92.2%) was similar to the overall probability of survival found in a studied that include HIV-infected children from 14 countries form Africa and Asia. [28]

The major proportion of regiments using NNRTs and the short median follow-up period might be due to more recent access to drugs and might reflect the high median survival rate (92,2%). However, both NNRTI-based regiment and PI-based regiment showed to be equally effective.

In this resource-limited setting, HAART was effective for HIV-infected children despite initiation of treatment during the advanced stage of disease or treatment of antiretroviral experimented subjects. Furthermore, the rates of HIV suppression measured by viral load tests showed similar to the rates found in international collaborative studies including developed and undeveloped countries [29,30].

Finally, the effectiveness of HAART use among children living at resource-limited setting should encourage global efforts to make ART available for all HIV-infected children in poor countries

Conclusion

Combination antiretroviral therapy for HIV-infected children living in resource-limited settings showed to be effective in reducing mortality, control burden of HIV viral replication and leading to immune restoration in the majority of patients.

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Table 1. Characteristics of all included studies

Study & publicat. Year	Design	Patients (n) Country	Median age (mon.)	Median baseline CD4 count/ percentage	Median baseline Viral Load	Treatment	Duration follow-up (months)	Outcome 1 Survival
Eley[5] 2006	Retrospec Descript	409 (South Africa)	23	11.7% (7%-17.3%) CD4 <15% = 66.2%	5.58 (5.14–6.11)	2 NRTIs + NNRTI or PI (naïve/non-naïve)	12	84% (80-87%)
Rouet[6] 2006	Longitud analysis	78 (Cote d'Ivoire)	78	7.5% (2.1%-11.1%)	5.37 (5.07–5.99)	2 NRTIs + NNRTI or PI (naïve)	42	86%
Zhang[7] 2007	Prospectiv Analysis	81 (China)	120 (naïve) 144 (exper)	*Naïve: 117 (24-186) Exper: 193 (97-342)*	Naïve: 5.53 (5.18-5.71) Exper: 4.85 (3.72-5.33)	AZT + 3TC + NVP	12	–
Reddi[8] 2007	Retrospect cohort study	151 (South Africa)	67	7.4% (2.1%-13.7%)	–	2 NRTIs + NNRTI or PI (naïve/non-naive)	12 (3.5-13.5)	90.9% (84.8-94.6)
O'Brien[3] 2006	Observat study	1184 (8 CRLS)	84	18-59m: 9.9% (6-13.2) *60-156m: 189.5 (73-339)*	–	2 NRTIs + NNRTI (naïve/non-naïve)	12	95%
Kline[9] 2007	Study popolation	414 (Romania)	156	*292 (1-1143)*	5.1 (<2.6-5.9)	Lopinavir/ Ritonavir containing HAART (naïve/non-naïve)	48	–
Song[10] 2007	Observat. Retrospect Study	29 (Kenya)	102	*182.3 (± 146.6)*	5.11 (± 0.72)	AZT + 3TC + NVP (naïve)	15	100%
Puthanakit[11] 2007	Descript Study	107 (Thailand)	91	5.3% (SD 4.9)	5.4 (SD 0.5)	2 NRTIs + NNRTI (naïve)	48	95%
Romanelli[12] 2006	Retrospec. observat. cohort study	43 (Brazil)	29.1 (Triple)	Triple: 20.1%(SD 9.3)	Triple: 5.6 (SD 0.8)	Triple teraphy: 2 NRTIs + NNRTI or PI	12	95.5%

						(naïve)			
George[13] 2007	Observat. study popolation	236 (Haiti)	75	12% (6%-19%)	5.3 (range:no data)	2 NRTIs + NNRTI ot PI (naive)	24	80%	+
Puthanakit[14] 2007	Prospectiv Observat.	192 (Thailand)	90	*171 (± 289)* 5.2% (± 4.9%)	5.4 (± 0.5)	2 NRTIs + NNRTI (naive)	12	94.3%	
Wamalwa[15] 2007	Prospectiv Observat	67 (Kenia)	52	*288 (101-560)* 6.2% (3.6%-10.3%)	18m-3y: 6.4 (6.0-6.6) > 3years: 5.8 (5.3-6.3)	2 NRTIs + NNRTI (naive)	6	91%	
Bolton-Moore[16] 2007	Open cohort assessment	4875 (Zambia)	81	12.9% (12.5-13.3%) *300 (138-551)*	–	2 NRTIs + NNRTI (naive)	24	–	
Machado[17] 2007	Longitud. Observat study	29 (Brazil)	69	*486 (7-2690)*	4.84 (3.0-5.7)	Previuos treatm without PI 13/29 (44.8%) Previuos treatm with PI 16/29 (55.2%) (non-naive)	12	–	
Jansaen[18] 2007	Observat. Cohort study	212 (Cambodia)	72	6% (2.6-13) *100 (22-273)*	–	d4T+3TC+NVP 68.9% d4T+3TC+EVF 18.8% AZT+3TC+NVP 12.3% (naïve/non-naive)	12	92%	
Lodha[19] 2005	Descriptiv Analysis	26 (North India)	69	*584 (± 685.9)*	–	D4T+3TC+NVP 57.6% AZT+3TC+NVP 29.6% d4T+ddI+NVP 7.6% (naïve)	6	96.2%	

Nyandiko[20] 2006	Retrospect review	279 (Kenya)	72	Orphans: 9% (1-33) *259 (4-942)* Non-orphans: 10% (1-41) *169 (4-1744)*	–	AZT+3TC+NVP child < 10kg d4T+3TC+NVP child > 10kg (naïve)	33 (orphaned) 41 (non-orph)	95%	
Puthanakit[21] 2005	Prospectiv Study	107 (Thailand)	NPV: 85.2 EFV: 102	**NVP** 4% (1-9%) ≤ *6 years: 61 (38-314)* > *6 years: 46 (30-103)* **EFV:** 3% (1-10%) ≤ 6 years: *228 (42-536)* > *6 years: 47 (21-128)*	NVP: 5.3 (± 0.5) EFV: 5.4 (± 0.4)	3TC+d4T+NVP Or 3TC+d4T+EFV (naive)	18	96.3%	21 53

6. SEGUNDO ARTIGO

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Long-term Follow-up Outcomes of Perinatally HIV-infected Adolescents: infection Control but School Failure

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Summary

Perinatally human immunodeficiency virus (HIV)-infected children are fighting acquired immune deficiency syndrome (AIDS) and becoming adolescents. The objective of this study was to examine long-term outcomes among perinatally HIV-1-infected adolescents. Cross-sectional clinical and laboratory data were collected for 49 perinatally HIV-infected adolescents followed at the *Instituto de Medicina Integral Prof. Fernando Figueira* (IMIP's) Hospital from 1987 to 2007. The mean age of these adolescents was 12.5 years, the majority were female (73.5%) with a mean follow-up duration of 9.0 years, 71.4% of adolescents had no signs of HIV infection, 81.6% had normal $CD4^+$ lymphocyte count, and 53.1% had undetectable HIV viral load. HIV disclosure to the adolescent was reported in 31 (63.3%) participants. The majority were in school (89.8%) but failure and drop-out were reported by 51% and 28.6% of the subjects, respectively. All five domains of quality of life (QOL) measured revealed high scores. The majority of long-term adolescent survivors showed HIV-infection control and high scores of QOL, but with problems in schooling functioning that need early detection and intervention.

Key words: AIDS, HIV infection, adolescence.

Introduction

The 2008 global acquired immune deficiency syndrome (AIDS) epidemic update estimates that 33 million (30–36 million) adults and children are living with HIV infection in the world with the higher prevalence rates among developing countries [1]. Brazil has identified 506 499 AIDS cases among adults and children from 1980 to June 2008 [2]. The five geographic regions of Brazil differ in their prevalence of human immunodeficiency virus (HIV) infection and in their degree of economic development. The northeast region holds 58 348 (11.5%) AIDS cases and is one of the most impoverished regions of the country. Besides this, some studies have already showed increased survival rates among adults and children even considering regional inequalities [3, 4]. Highly active antiretroviral therapy (HAART) is considered the main factor behind the improvement of survival rates among HIV-infected children and adolescents [5]. Brazilian AIDS patients have free access to treatment, both antiretroviral and opportunistic infections drug therapy [6–8]. The access to HAART resulted in a significant reduction of opportunistic infections, hospitalizations, and deaths among HIV-infected Brazilian children and adolescents [9,10].

Accordingly, course and prognosis of paediatric HIV infection has been transformed. Perinatally infected children are becoming adolescents and now living into adulthood. This change has brought with it unexpected challenges such as the maintenance of treatment adherence [11], long-term side-effects [12], HIV disclosure status (e.g. to friends, schoolmates, sexual partners) and psychosocial adjustment [13], school-related issues [14], and other quality of life (QOL) issues [15, 16, 20].

Despite the great therapeutic success in controlling HIV infection, AIDS is still associated with factors that could interfere in lifetime treatment efficacy and quality of life. Indeed, some studies were done in this area among adults and children [21, 22]; however, they did not focus on perinatally HIV-infected adolescents. Therefore, the present study aimed to describe socio-demographic, clinical, and laboratory characteristics and QOL among a cohort of perinatally HIV-infected adolescents

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followed up at a tertiary health-care centre in north-eastern Brazil.

Materials and Methods

Study population

The study population consisted of perinatally HIV-infected adolescents in the age range of 10–19 years (World Health Organization (WHO) definition) enrolled at the *Instituto de Medicina Integral Prof. Fernando Figueira* (IMIP)'s Hospital HIV Infection Clinic (HIC-IMIP) from July 2006 to June 2007. This public clinic has followed up 256 children and adolescents since 1987, with most individuals coming from a low-income urban population. The HIC-IMIP is a national reference for the treatment of HIV infection and has a team of health-care professionals (e.g. physicians, nurses, psychologists, dentists) and a day-care hospital unit.

Adolescents and their parents/caregivers/guardians accompanying them were contacted during a scheduled medical visit with the purpose of obtaining their consent to participate in the current study. Patients had to be on HAART treatment for at least 6 months. Patients with other underlying health conditions (e.g. congenital heart disease, chronic renal disease) and sexually infected HIV adolescents were excluded from our study.

Study design

This cross-sectional study was conducted with two approaches. First, we used cross-sectional data from a cohort of HIV patients followed up at IMIP's hospital since 1987. These data included epidemiologic, clinical, and laboratory findings at baseline and at the last medical visit. Socio-demographic variables included age at the Center for Disease Control and Prevention (CDC)-defined AIDS diagnosis, gender, where/with whom he/she lives, schooling, HIV disclosure, social welfare benefits, and non-governmental organization support. Clinical and laboratory indicators of severity of disease were evaluated at baseline (classification at admission) and at the last medical visit (current classification) using the CDC classification system [23]. Efficacy of therapy and HIV-infection control were defined as undetectable viral loads (HIV-RNA plasma levels <400 copies/ml) during the last 3 months).

Secondly, we interviewed parents/guardians/caregivers for QOL measurements. For this we translated and had a pilot-testing version of the Quality of Life Assessment – Revised (for ages 12–20 years), developed by the Division of AIDS of the National Institute of Allergy and Infectious Diseases – National Institutes of Health, US. This QOL assessment consists of five domains that include health perceptions, physical functioning, psychological functioning, social/school functioning, and HIV symptoms. Each of these domains have been already described elsewhere [15, 16]. Interviews took on average 25–30 min.

Statistical analyses

Descriptive statistics were used to characterize the socio-demographic, clinical, and laboratory variables. Comparison between adolescent characteristics and viral load status were examined by using the *t*-test for continuous variables whereas chi-square and Fisher's exact tests were used for categorical variables. Analysis of Variance (ANOVA) was used to perform exploratory data analysis. To measure the internal consistency of the means of the QOL items, we used Cronbach's alpha. Univariate and multiple logistic regressions were used to identify independent factors associated with HAART success or failure. All analyses were performed with Statistical Package for the Social Sciences (SPSS) version 12 and EpiInfo version 3.4.3, and using two-tailed tests, and p-values <0.05 were considered significant.

Results

On the basis of the inclusion/exclusion criteria, 49 out of 56 perinatally HIV-infected adolescents participated in this study. Patients who changed therapy due to HAART failure were using mostly a protease inhibitor (PI)-HAART-based regimen. As shown on Table 1, the mean age of the adolescents was 12.5 years (min: 10, max: 19; WHO definition), the majority were female (73.5%), and the mean age when initiating follow-up at IMIP's HIC was 3.8 years (min: 0, max: 11) with a mean follow-up period of 9.0 years (min: 2, max: 18). All participants were using HAART since a mean age of 4.9 years (min: 0, max: 12), 46.9% were using the first HAART regimen, 69.4% of subjects reported 100% treatment adherence in the last 3 months, and 46.9% had some HAART-related side-effect. At the moment of admission to the clinic, 67.3% of the patients were classified as category B and C. Clinical and laboratory data collected during the last medical visit (i.e. last 3 months) showed that 71.4% of adolescents did not have any signs of HIV infection (CDC category N), 81.6% had a normal $CD4^+$ lymphocyte count [CDC category 1, mean: 765.8 (min: 22, max: 1706)] and 53.1% had undetectable HIV viral load level (<400 copies of HIV RNA/ml).

The majority of adolescents lived with their families (87.6%) in the metropolitan area of Recife (83.7%). As shown in Table 2, guardians/caregivers/parents were illiterate in 10 cases (20.4%) and had <8 schooling years in 24 cases (49%). They were the biological mothers in 15 cases (30.6%) and the biological father in nine cases (18.4%). In addition, 55.7% of the subjects had a family member living

TABLE 1
socio-demographic, clinical and laboratory data of 49 perinatally HIV-infected adolescents according to viral load, i.e. <400 copies ml^{-1} (n=26) or >400 copies ml^{-1} (n=23)

Characteristics	Viral load			*p*-value*
	All participants	≤400 copies	>400 copies	
Age, mean (SD), years	12.5 (2.3)	12.5 (2.3)	12.5 (2.4)	0.974
Gender, Female *N* (%)	36 (73.5)	19 (73.1)	17 (73.9)	0.947
Age at the initiation of follow-up, mean (SD), years	3.8 (2.7)	4.5 (3.0)	3.0 (2.0)	0.050
Duration of follow-up, mean (SD), years	9.0 (3.5)	8.4 (3.3)	9.8 (3.7)	0.167
Age of first HAART, mean (SD), years	4.9 (2.9)	5.6 (2.9)	4.2 (2.7)	0.099
Using first HAART regimen, *N* (%)	23 (46.9)	17 (65.4)	6 (26.1)	<0.01
100% Adherence, *N* (%)	34 (69.4)	18 (69.2)	16 (69.6)	0.980
Any HAART-related side-effect, *N* (%)	23 (46.9)	11 (42.3)	12 (52.2)	0.490
CDC clinical category B and C at admission, *N* (%)	33 (67.3)	16 (61.5)	17 (73.9)	0.357
Current CDC clinical category N, *N* (%)	35 (71.4%)	25 (96.2)	10 (43.5)	<0.01
Current CDC immunological category, *N* (%)	40 (81.6)	24 (92.3)	16 (69.6)	<0.01
Current CD4+ cells count, mean (SD)	765.8 (397.6)	876.8 (295.5)	640.2 (463.2)	0.036

SD, standard deviation; HAART, highly active antiretroviral therapy; CDC, centres for diseases control and prevention.
**p*-value from univariate analysis.

TABLE 2
Social and role functioning and QOL domain scores for the 49 perinatally HIV-infected adolescents according to viral load, i.e. <400 copies mL^{-1} (n=26) and >400 copies mL^{-1} (n=23)

Characteristics	Viral load			*p*-value*
	All participants	≤400 copies	>400 copies	
Care by biological mother, *N* (%)	15 (30.6)	11 (42.3)	4 (17.4)	0.059
Care by biological father, *N* (%)	9 (18.4)	2 (7.7)	7 (30.4)	0.064
Other family member living with HIV, *N* (%)	27 (55.7)	15 (57.7)	11(47.8)	0.490
Death of family member due to AIDS, *N* (%)	32 (65.3)	16 (61.5)	16 (69.6)	0.556
Social welfare benefits, *N* (%)	26 (53.1)	16 (61.5)	11 (47.9)	0.336
HIV disclosure, *N* (%)	31 (63.3)	15 (57.7)	16 (69.6)	0.390
Age at HIV disclosure, mean (SD)	7.3 (3.4)	7.2 (2.8)	7.5 (4.0)	0.847
School attendance, *N* (%)	44 (89.8)	24 (92.3)	20 (87.0)	0.655
School failure, *N* (%)	25 (51.0)	12 (46.2)	13 (56.5)	0.469
School dropout, *N* (%)	14 (28.6)	8.0 (30.8)	6.0 (26.1)	0.717
HIV disclosure to school staff, *N* (%)	17 (38.6)	8.0 (33.3)	9.0 (39.1)	0.429
Discrimination due to HIV, *N* (%)	18 (36.7)	9.0 (34.6)	9.0 (39.1)	0.744
Friend's knowledge about HIV, *N* (%)	15 (30.6)	7.0 (26.9)	8.0 (34.8)	0.551
Friendship change, *N* (%)	6 (17.1)	0	6 (35.3)	<0.01
Health perceptions (0–10), mean (SD)	9.0 (1.6)	9.5 (1.0)	8.6 (2.0)	0.050
Physical functioning (SD)	9.1 (1.3)	9.3 (1.3)	8.9 (1.3)	0.300
Psychological functioning (0–10), mean (SD)	8.5 (2.0)	9.0 (1.5)	7.9 (2.3)	0.037
Social/school functioning (0–10), mean (SD)	8.2 (2.2)	8.2 (2.3)	8.1(2.1)	0.971

SD, standard deviation; *N*, number. **p*-value from univariate analysis.

with HIV and 65.3% had lost family members due to AIDS. Support by social welfare was reported by 26 adolescents (53.1%). HIV disclosure to the child was present in 31 (63.3%) participants and occurred at 7.3 years of age (min: 1, max: 16). Three adopted children had HIV disclosure before their third year of life. The majority of patients were attending school (89.8%) but the school staff were informed about HIV status in only 38.6% of the cases. School failure and school drop-out were reported by 51 and 28.6% of the subjects, respectively. More than a third of adolescents (36.7%) reported being discriminated due to HIV. Disclosure of HIV status to friends was described by 36.7% of the caregivers/

guardians/parents and they believe that this disclosure changed their friendships in 17.1% of the cases. Client satisfaction with health-care services provided at IMIP's HIV Clinic was high, with only one guardian not being satisfied with it (2.0%).

All five domains of QOL measured revealed high scores with the highest score (9.1) being for physical functioning and lowest score (8.2) for social/school functioning ($p < 0.05$). Cronbach's alpha score for this psychometric instrument was high (0.73).

Children who achieved therapeutic success as measured by viral suppression (viral load <400 copies/ml) were more likely to be classified in clinical categories N or A, to have no immune suppression, to use a first HIV regimen, and to have higher scores on health perceptions and psychological functioning QOL domains (assessed by univariate and logistic regression analyses). Having more advanced clinical symptoms at the moment of AIDS diagnosis (categories B or C) was not associated with success or failure of HAART. However, having the biological father as a caregiver was associated with a higher likelihood of presenting with treatment failure (as shown by multivariate logistic regression).

Discussion

Most study subjects were young adolescents (mean age: 12.5 years). This younger population is explained by the fact that we are now dealing with the first generation of children born with HIV reaching adolescence. Another retrospective longitudinal study involving 108 perinatally HIV-infected adolescents found similar results [24].

Almost three-quarters (73.5%) of all adolescents in our sample were female. There is conflicting data regarding gender and HIV disease progression, HAART adherence, and mortality among the adult HIV-infected population [25–27]. Gender differences are also not yet fully understood in paediatric AIDS patients [28, 29]. Thus, a higher prevalence of perinatal HIV infection among girls and a lower progression rate may explain our findings.

The mean age at diagnosis/start of follow-up (~4 years) and being classified as categories B and C might reflect delays on prompt HIV-infection suspicion and AIDS diagnosis [30]. All patients started HAART following AIDS diagnosis and most of them (69.4%) reported 100% adherence to treatment in the last 3 months. These findings indicate that strict adherence to HAART is feasible at resource-limited settings although there is an ongoing challenge of maintaining adherence as children mature through adolescence. High-level of HAART adherence and treatment success were reflected in the clinical and laboratory outcome parameters evaluated in this group of adolescents.

Most of the socio-demographic characteristics of our study sample are representative of the population of children and adolescents (HIV-infected or not) followed up at IMIP's Hospital [31]. Most of them live in the Recife metropolitan area and have non-biological guardians with low levels of literacy. Furthermore, almost half of the adolescents who had a biological parent as the primary caregiver, differed in the impact on adherence of having an adult other than the biological parent as the primary caregiver [32].

Half of the adolescents in our sample receive social welfare benefits because of their illness. In Brazil, these benefits correspond to the minimum monthly wage received by civil servants. There is a concern about the psychosocial impact on healthy adolescents of receiving this benefit and the potential social advantages associated with it [33]. Data exploration for associations between receiving social welfare benefit and levels of school attendance and failure did not reveal any significant association. However, receiving the social benefit was associated with an increased proportion of school drop-out ($p = 0.024$).

The proportion of HIV disclosure to the child/adolescent (as reported by guardians) was moderate (63.3%) and clearly needs to be enhanced. Additionally, the disclosure to friends had some psychosocial impact (altered friendship) [34]. Disclosure of HIV status to the child has been shown to be a good strategy to promote adherence but this was not demonstrated by our study [35].

School attendance was high (89.8%), but five adolescents were not attending school and this was not associated with health problems. Our results are similar to those reported by the few studies designed to explore educational and psychosocial aspects in children with HIV infection [36]. This high proportion of school failure rates might be due to the relationship between perinatal HIV infection and neurocognitive impairments but there are conflicting data on this issue [37–39]. However, a recent study engaging 9–16-year-old youths found poor language ability among HIV-infected youth [40]. On the other hand, low levels of caregiver education and high local prevalence of school failure and drop-out might act as confounders when it comes to school performance and attendance. However, the follow-up of these adolescents since childhood by a multi-professional team ought to have detected school problems at an early stage.

The high scores in all five domains of QOL display the well-being felt by this group of adolescents. Furthermore, antiretroviral treatment appears to have the potential of improving QOL among HIV-infected children and adolescents [15, 16].

Finally, we consider the high rates of self-reported adherence and, as a result, the elevated proportion of perinatally HIV-infected HIV adolescents who achieved and maintained long-term treatment success and attained high scores of QOL a clinical success. However, we need to improve HIV disclosure to

the adolescents and be aware of school-related problems. Practices regarding the prevention and early recognition of school failure should be put into action by all health professionals dealing with HIV-infected youth and our recommendation is that this should be done at every HIV-clinic visit as part of their long-term follow-up.

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7. TERCEIRO ARTIGO

7. Tilte: Predictors of long-term antiretroviral therapy effectiveness among HIV-1 infected children in a hybrid scenario: does gender matter?

Title Page:

Title: Running head: HAART in children: does gender matter?

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Abstract

Objective: To evaluate the effectiveness and durability of highly active antiretroviral therapy (HAART) in perinatally HIV-1 infected children and adolescent and to identify predictors successful therapy.

Design: Historical cohort study.

Setting: IMIP´s AIDS clinic, leading paediatric HIV centre in a tertiary health care hospital in Recife, Pernambuco State, Brazil.

Participants: A total of 195 children and adolescents with perinatally acquired HIV infection.

Main outcome measure: Response to HAART and its durability.

Results: At the end of the follow-up, 102/195 (52.3%) had successful response to HAART with a mean time of any HAART use of 4.9 (SD, 2,5; min. 0.7, max. 9.9) years. After adjustment for baseline and HAART factors, success treatment outcome was inversely associated with male gender (odds ratio, OR = 0.5, p = .029), associated with living in Recife Metropolitan Area (RMA) (OR = 2.8, p = .017), strongly associated with patients/caregiver who were adherent by physician judgment (OR =19.6, p < .001)). Additionally, the time to failure of 1st HAART was negatively associated with male gender (relative hazard, RH=0,5, p = .021) and living out of RMA (RH= 0.4, p = .009), and associated with CDC immunological stage 1 (RH=2.9, p = .003) and patients who were adherent by physician judgment (RH =2.2, p = .003).

Conclusions: HAART effectiveness and durable response was associated with gender, living location, degree of immunodeficiency and with adherence to HAART.

Key-words: HIV, highly active antiretroviral therapy, children, adolescent, treatment.

Introduction

The 2008 global AIDS epidemic update estimates that 33 million [30-36 million] of adult and children are living with HIV infection in the world with the higher prevalence rates among developing countries [1]. Brazil has identified 506,499 AIDS cases among adults and children from 1980 until June 2008 [2]. The five geographic regions of Brazil differ in their prevalence of human immunodeficiency virus (HIV) infection and in their degree of economic development. The North-East region holds 58,348 (11.5%) AIDS cases and is one of the most impoverished regions of the country. The State of Pernambuco (1982-2008) comprises 14,308 AIDS cases, 66.8% of subjects are male, 83.7% non-white, 7.5% are illiterate and 54% has < 8 schooling years. From the total Pernambuco AIDS cases, there are registered 306 AIDS cases in children < 13 years of age and the acquisition of HIV was identified as mother-to-chilld HIV transmission. Besides this, some studies have showed increased survival rates among adults and children even considering regional inequalities [3,4].

Highly active antiretroviral therapy (HAART) is considered the main factor behind the improvement of survival rates among HIV-infected children and adolescents [5]. Brazilian AIDS patients have free access to HIV infection laboratory measures (*i.e*. HIV RNA level and CD4+ T lymphocyte count) and treatment, both antiretroviral and opportunistic infections drug therapy [6-8]. All Brazilian HIV clinics need to follow the national guidelines on the management of HIV infection to have access to laboratory test and to antiretroviral drugs. The universal access to HAART resulted in a significant reduction of opportunistic infections, hospitalizations, and deaths among HIV-infected Brazilian children and adolescents [9,10].

Previous clinical and observational studies on the efficacy and safety of antiretroviral treatment regimens have been conducted in cohorts of HIV infected children living in developed countries and in resource-limited settings [11-15]. However, long-term effectiveness studies considering as endpoints immunological and virological factors, as well morbidity and mortality, rely on studies done in developed countries. This might be due too delay in the access to antiretroviral drugs in resource-limited settings. Recently (2008), Patel et al. in a 10- year follow-up study including

1,236 perinatally HIV infected children and adolescents and using a weighted Cox regression model adjusted for time-varying confounding by severity, showed that the use of HAART was highly effective in reducing HIV related mortality [16]. Additionally, Van der Borght et al. (2009) evaluating the effectiveness of an HIV workplace programme in sub-Saharan Africa found over the first 5 years of the programme that long-term high survival was achieved [17]. In Brazil, Candiani et al. (2007) studying HIV infected children in Minas Gerais State, Southeastern demonstrated the effectiveness of HAART in significantly reducing opportunistic infections, hospitalizations, and deaths in this Brazilian setting cohort [18].

To increase current knowledge, we therefore aim to evaluate the responses to HAART regimens (effectiveness and durability) and identify predictor factors among perinatally HIV-1 infected children and adolescents living in hybrid scenery, full access to treatment in a resource limited setting.

Materials and Methods

Study Population

The eligible population for this study consisted of 256 participants with 25 (9.7%) registered deaths. However, the studied population consisted of 195 patients with 11 (5.6%) deaths. All were HIV infected children and adolescents followed at IMIP´s Hospital HIV Infection Clinic (HIC-IMIP) from September 1987 until December 2007 with complete records data and meeting inclusion criteria, *i.e* have at least 6 months of HAART.

Study Design

We conducted a historical cohort study to determine the effectiveness of HAART in HIV infected children and adolescents followed at HIC-IMIP. We studied sociodemographic features of the study subjects and their primary caregiver and other potential factors that might interfere in treatment responses.

This study was approved by the human subjects review board of the IMIP´s Hospital.

Procedures and follow-up

Patients were admitted into HIC-IMIP mostly subsequent to the HIV/AIDS diagnosis duration hospitalization or from paediatric out-patient department. At the admission, sociodemographic data were collected and categorized as age at HIV/AIDS diagnosis $\leq$ or > 2 years, ethnicity in white and non-white, living area Recife metropolitan area or other areas of Pernambuco State. HIV infection or AIDS clinical diagnosis was done by physicians according to the National Paediatric AIDS Case-Definition [19], with clinical and laboratory evaluation for classification of HIV disease using the Centers for Diseases Control and Prevention (CDC) criteria [20]. For analysis purpose, we arranged as stage N/A or B/C and immunological classification as stage 1 or 2/3, CD4+ T cell absolute count as $\leq$ or > 750 cells/mL and HIV RNA measurements (viral load) as $\leq$ or > 100.000 copies of HIV RNA/mL. HIV RNA measurements and CD4+ T lymphocyte count were included in the study before or during the diagnosis of AIDS and around 24 and 48 weeks.

HAART regimen was available since 1996. Antiretroviral exposure before introduction of HAART was defined as mono and dual antiretroviral therapy. First HAART was defined as the use of 3 antiretroviral of 2 classes, 2 nucleoside reverse transcriptase inhibitors (NRTI) + either 1 non-nucleoside transcriptase inhibitor (NNTRI) or protease inhibitor (PI).. Effectiveness to HAART was defined as undetectability of HIV level by the moment HIV RNA threshold standard, either < 400 copies of HIV RNA/mL formerly and < 50 copies of HIV RNA/mL latterly. Patients had to be on HAART treatment for at least 6 months. Adherence was measured by the two physician's view that followed all patients and categorized them as adherent or not adherent. Primary caregiver was categorized as biological parent or not biological parent and had their schooling years registered if they were literate. HAART effectiveness was categorized as success or failure based respectively in detection or no detection of blood HIV RNA copies/mL at the last measurement during follow-up (death, lost of follow-up, emigration or alive). Duration of effectiveness of first HAART was measured as the time between initiation of HAART until confirmation of virological failure after at least 24 weeks of antiretroviral use. We also studied the use of trimethoprim/sulfamethoxazole and/or intravenous immune globulin (IVIG) and the duration of use measured as the time from starting to withhold.

Statistical Analyses

Descriptive statistics (means with standard deviations and median with inter quartile ranges) were used to characterize the sociodemographic, clinical e laboratory variables. Comparison between adolescent characteristics and response to HAART was examined by using *t* test for continuous variables whereas chi-square and Fisher´s exact tests for categorical variables. Mann-Whitney test was used to compare and explorer data. Multiple logistic regressions models were used to identify prognostic factors associated with treatment success. Cox proportional hazards models were used for analysis of the length of 1st HAART effectiveness relating with covariates and significance was determined by Likelihood Ratio test. Data were analysed with SPSS version 12 and EpiInfo version 3.4.3, and using two-tailed *P* values when < .05 was considered significant.

Results

On the basis of the inclusion/exclusion criteria and complete data records, 195 perinatally-infected HIV children and adolescents participated in this study. Seven patients (3.6%) died and 9 (4.6%) were lost/emigrated during follow-up period.

The baseline and follow-up characteristics of the study participants according to the main outcome (HAART success or failure) at the time of the end of follow-up (death, lost, emigrated or alive) are presented in the TABLE 1. The mean time of any HAART use was 4.9 (SD, 2,5; min. 0.7, max. 9.9) years and was not different according to treatment outcome (p = .581). At baseline, the median age at AIDS diagnosis was 2.7 years (interquartile range (IQR), 0.1-5.1) and 93 (47.7 %) were < 2 years of age, 101 (51.8%) were female, 154 (79.0%) were non-white, 149 (76.4%) were living at Recife Metropolitan Area (main urban area of Pernambuco State), 145 (74.4%) had CDC clinical stage B or C, 143 (73.3%) had CDC immunological stage 2 or 3, with median 620 (277-1096) absolute CD4+ T cell count, 106 (54.4%) with $\leq$ 750 cels/ml and 80 (41.0%) with > 100.000 HIV-1 RNA copies/ml.

The primary caregiver was biological for 131 (67.2%) of the study participants, had median 6.0 (IQR, 4.0-9.5) schooling years and 23 (11.8%) were illiterate. Previous antiretroviral exposure was detected in 36 (18.5%) participants and were mono (zidovudine, ZDV) or dual (ZDV + didanosine or lamivudine) therapy, 118 (60.5%) used a 1st HAART regimen containing NNTI and 132 (67.7) were considered adherent to treatment by their physician.

Change in HAART regimen was done in 98 (50.3%) of the study participants and 48 out of 176 the regimen change was to improve adherence. At the end of follow-up, 102 (52.3%) of children and adolescents full field criteria of success treatment outcome (viral load below detection threshold). *Pneumocystis jiroveci* prophylaxis with trimethoprim/sulfamethoxazole was used by 177 (90.8%) of the participants with mean 4.0 (3.2) years to withhold. Additionally, intravenous immune globulin was prescribed to 159 (81.5%) of the patients for median 2.6 (IQR, 1.1-4.9) years.

In the bivariate analysis, the percentage of children and adolescents who were female, were living at RMA, were antiretroviral drugs naïve and were adherent by their physician judgement was significantly higher in the success treatment outcome group. We included in the logistic regression model all potential predictor variables with p value $\leq .25$ as well as age at AIDS diagnosis. Logistic regression, after adjustment for baseline and HAART factors, showed that success treatment outcome was inversely associated with male gender (odds ratio, OR= 0.5, p = .029), was associated with living in RMA (OR= 2.8, p = .017), and strongly associated with patients/caregiver who were adherent by physician judgment (OR = 19.6, p < .001), as shown in TABLE 3.

The median time to 1st HAART failure was 3.5 (IQR = 2.2-6.7; min. 0.6, max. 9.9) years with no difference between the two HAART outcome groups (p=.080). TABLE 2 summarizes the time-varying predictors of length of 1st HAART success (censored) until HAART failure (event) by Cox proportional hazard analysis.

After adjustment for subject characteristics, baseline and HAART related factors, time for 1st HAART failure was inversely associated with male gender (relative hazard, RH = 0.5, p = .021) and living out of RMA (RH = 0.4, p = .009), and associated with CDC immunological stage 1 (RH = 2.9, p = .003) and patients who were adherent by physician judgment (RH = 2.2, p = .003) and weakly associated with having viral load < 100.000 HIV-1 RNA copies/m (p = .06). The male (female) overall accumulative probability of failure to HAART at 1, 3 and 5 years was 4% (2%), 22%/13% and 38%/23%, respectively (**Fig. 1**). Based in multivariable analysis, either logistic regression or Cox proportional hazards analysis, female gender, location, CDC immunological stage 1 (without immunodeficiency) and adherence to treatment were associated with HAART effectiveness (success and durability), presented in TABLE 3.

Discussion

Our results showed that HAART was effective in suppression of viral load in 52,3% of children and adolescents with a mean time of 4.9 years. This viral suppression rate is lower than found in studies done in Europe. Chiappini et al, studying a group of 40 perinatally HIV-infected children receiving early HAART with a median follow-up period of 5.96 years, found that 77,5% reached undetectable viral at the last visit [21]. However, early HAART appears to be more successful [22]. Bracher L et al following 49 perinatally infected children treated with HAART during 10 years (1996-2005) found that approximately 60% achieved undetectable viral load within the first weeks of therapy and this remained stable for up to 8 years [23] Data from resource limited settings, although with less time of follow-up, shows similar rates of viral suppression. Jaspan et al studying 391 children treat with HAART found that 49% with virological suppression at 24 months [24]. Furthermore, our results highlight gender, location, baseline immunological stage and adherence as predictors of durability and HAART effectiveness among HIV-1 infected children and adolescents in a hybrid scenario setting at Pernambuco, Brazil.

HAART effectiveness and durable response to HAART was associated with being female by both adjusted multivariable analysis model (logistic regression and Cox proportional hazard). There is conflicting data regarding gender and HIV disease progression, HAART adherence and mortality among the adult HIV-infected population [25-27]. However, a systematic review recently published by Nicastri (2007) stress that although few clinical studies showed a significantly better virological response in women compared with men, recent clinical and observational trials suggest a better clinical outcome for women. Gender differences are also not yet fully understood in paediatric AIDS patients [28-30]. We previously studied 49 long-term perinatally HIV-infected adolescents followed at IMIP´s Hospital and found that their mean age was 12.5 years and that the majority were female (73.5%) with a mean follow-up period of 9.0 years [31].

Living at Recife metropolitan area was associated with either success to any HAART and its durability. Several difficulties that influences adherence have been

reported in Brazil, including living location, and nonadherence have become a challenger to health professional teams that works with patients with HIV infection [32].

Some studies have already shown the association of better HAART response with less HIV-1 associated immunodeficiency and lower HIV RNA viral load at diagnosis and before starting HAART [33,34]. All results follow these scientific evidences.

Adherence to treatment is strictly associated with HAART response everywhere [35-37]. We included in this study the physician opinion of patient/caregiver adherence to HAART. The physician opinion was based in subjective aspects associated with previous laboratory evaluations (including CD4+ T cells count and HIV viral load). The latter must be the main factor of the association found in this study. However, in a setting where is difficult to access adherence, this approach showed to be feasible and without requiring additional time or cost.

In conclusion, our finding on gender differences and HAART durability and response among long-term perinatally HIV-1 infected children and adolescents bring up some questions about the reasons of these differences that will need further clarification and future research studies. Reasonably, we might suppose that some factor might be involved as: genetic, biological, pharmacological or sociocultural contexts. For while, we strictly recommend more efforts in treatment adherence of both gender and some extra effort when we are dealing with a male patient.

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There are no conflicts of interests.

TABLE 1. Baseline and follow-up characteristics of HIV-1 infected children adolescent followed at IMIP´s AIDS Clinic (1987-2007)

Characteristics	*Treatment outcome No (%)*			
	All participants n=195	*Success n=102(52.3)*	*Failure n=93(47.7)*	*P value**
Age at AIDS diagnosis (HIV+), < 2 years, No (%)	93 ((47.7)	50 (53.8)	43 (46.2)	.760
Gender, female, No.(%)	101 (51.8)	60 (59.4)	41 (40.6)	.040
Ethnicity non-white, No (%)	154 (79.0)	77 (50%)	77 (50%)	.211
Living at RMA, No (%)	149 (76.4)	85 (57.7)	64 (43.0)	.017
CDC clinical stage B or C, No (%)	145 (74.4)	73 (50.3)	72 (49.7)	.350
CDC immunological stage 2 or 3, No (%)	143 (73.3)	74 (51.7)	69 (48.3)	.795
CD4+ cells count, ≤ 750 cells/mL, No (%))	106 (54.4)	55 (51.9)	51 (48.1)	.852
HIV-1 viral load (> 100.000 copies/mL), No (%)	80 (41.0)	38 (47.5)	42 (52.5)	.360
Caregiver (biological parent), No (%)	131 (67.2)	67 (51.1)	64 (48.9)	.642
Caregiver schooling, median (IQR), years	6.0.(4.0-9.5)	6. (4.0-10.0)	5 (4.0-9.0)	.165
Illiterate primary caregiver, No (%)	23 (11.8)	9 (39.1)	14 (60.9)	.154
Previously ARV therapy, No (%)	36 (18.5)	13 (36.1)	25 (63.9)	.032
HAART regimen (2 NTRIs + 1 NNTRI), No (%)	118 (60.5)	66 (55.9)	52 (44.1)	.210
Adherence (physician view), No (%)	132 (67.7)	94 (71.2)	38 (28.8)	<.001
HAART regimen changed, No (%)	98 (50.3)	46 (47.0)	52(53.0)	.086
Time to 1st HAART failure, median (IQR)	3.5 (2.2-6.1)	4.1 (2.4-6.7)	3.3 (2.1-5.3)	.080
P. jiroveci prophylaxis (PJP), No (%)	177 (90.8)	92 (52.0)	85 (48.0)	.772
Time to withhold PJP, mean (SD), years	4.0 (3.2)	3.3 (2.6)	4.8 (3.7)	.009
IVIG use, No (%)	159 (81.5)	86 (54.1)	73 (45.9)	.296
Time to withhold IVIG, median (IQR), years	2.6 (1.1-4.9)	2.3 (1.2-3.9)	3.3 (0.9-5.9)	.115

RMA, Recife metropolitan area; CDC, centres for diseases control and prevention; IQR, interquartile range; ART, antiretroviral; HAART, highly active antiretroviral therapy; NTRIs, nucleoside reverse transcriptase inhibitors; NNRTI, Non-nucleoside reverse transcriptase inhibitor; SD, standard deviation; IVIG; intravenous immune globulin.
* P-value from bivariate analysis was alculated by Mann-Whitney and Pearson´s Chi-square tests.

TABLE 2. Estimated effects of baseline and follow-up characteristics of HIV-1 infected children adolescent followed at IMIP´s AIDS Clinic (1996-2007) on time of 1st HAART failure.

Characteristics	*Hazard Ratio (95% CI)*	*P**
Age at AIDS diagnosis		
< 2 years	Referent	
> 2 years	1.22 (0.73-2.03)	.444
Gender		
Female	Referent	
Male	0.60 (0.37-0.97)	.038
Ethnicity		
White	Referent	
Non-white	1.71 (0.91-3.20)	.095
Living Area		
Other areas	Referent	
RMA	0.61 (0.30-1.24)	.174
CDC clinical stage		
N and A	Referent	
B and C	1.39 (0.75-2.55)	.294
CDC immunological stage		
1	Referent	
2 and 3	2.87 (1.46-5.68)	.002
CD4+ T cells count		
≤ 750 cells/mL	Referent	
> 750 cells/mL	0.65 (0.38-1.11)	.118
HIV-1 viral load		
≤ 100.000 copies/mL	Referent	
> 100.000 copies/mL	1.7 (0.98-2.84	.058
Caregiver		
Biological	Referent	
Non-biological	1.0 (0.61-1.71)	.929
Caregiver schooling years		
< 4 years	Referent	
> 4mean	0.96 (0.51-1.79)	.888
Illiterate primary caregiver		
Yes	Referent	
No	0.83 (0.42-1.65)	.590
Adherence (physician view)		
Yes	Referent	
No	2.95 (1.82-4.78)	< .001
1st HAART regimen		
2 NTRIs + 1 NNTRI	Referent	
2 NTRIs + 1 IP	1.20 (0.72-1.99)	.480
HAART Effectiveness		
Yes	Referent	
No	2.59 (1.56-4.29	<.001

RMA, Recife metropolitan area; CDC, centres for diseases control and prevention; HAART, highly active antiretroviral therapy; NTRIs, nucleoside reverse transcriptase inhibitors; NNRTI, Non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor;

* P-value Cox proportional hazards was calculated by Likelihood Ratio test.

TABLE 3. Final adjusted effects of baseline and follow-up characteristics of HIV-1 infected children adolescent followed at IMIP´s AIDS Clinic (1996-2007) on HAART success and durability.

Characteristics	*Success*		*Durability (time to failure)*	
	OR (95% CI)	*p*	*RH (95% CI)*	*p*
Gender				
Male	0.5 (0.2-0.9)	.029	0.5 (0.3-0.9)	.021
Living Location				
RMA	2.8 (1.2-6.3)	.017		
Other areas			0.4 (0.3-1.2)	.009
CDC immunological stage				
1 – without ID			2.9 (1.4-5. 8)	.003
Adherence				
Yes	19.6 (8.2-47.2)	<.001	2.2 (1.3-3.5)	.003

OR, odds ratio; RH, relative hazard; RMA, Recife metropolitan area; CDC, centres for diseases control and prevention; ID, immunodeficiency. (-), variable that do not enter in the model (p > .25).

* P-values were calculated by Logistics Regression and Cox proportional hazards analysis.

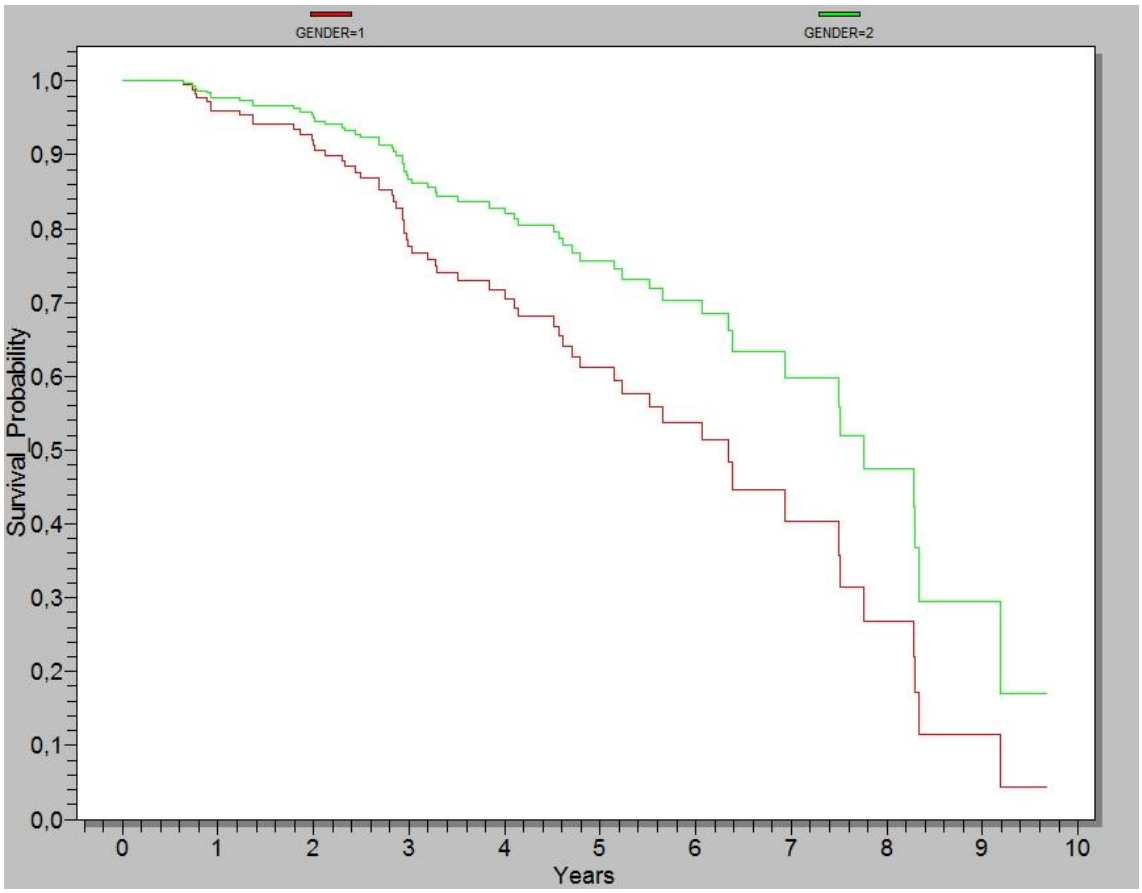

Figure 1. Estimated effect of gender on effectiveness of 1st HAART in children and adolescents followed at IMIP´s AIDS Clinic (1996-2007). Gender 1 = male; gender 2 = female.

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10. CONSIDERAÇÕES FINAIS

10. Considerações finais

Conclusões

As crianças infectadas pelo HIV de países com recursos escassos respondem à terapia antirretroviral tão bem quanto às crianças de países desenvolvidos. Apesar de iniciarem tratamento mais tardiamente e com doenças mais avançada.

Os adolescentes infectados pelo HIV por transmissão vertical, sobreviventes de longa duração do SAE-HD do IMIP, são na sua maioria do sexo feminino, atingem a adolescência clinicamente bem, com contagem normal de linfócitos T CD4+ e controle virológico. Adicionalmente, apresentam altos escores em cinco domínios de questionário de qualidade de vida. Contudo, apesar de todos estes parâmetros anteriores, apresentam altas taxas de falha no rendimento escolar e evasão escolar.

Crianças e adolescentes infectados pelo HIV e acompanhados em serviço localizado em cenário híbrido, *i.e.* acesso total a medicamentos e exames de alta complexidade mas vivendo em situação de recursos escassos, apresentam boa resposta terapêutica ao uso de drogas antirretrovirais. Contudo, com maior chance de atingir e manter sucesso terapêutico quando são do gênero feminino, quando moram próximo ao serviço, quando são consideradas aderentes ao tratamento e quando iniciaram tratamento sem dano imunológico (categoria imunológica 1, classificação do CDC).

Sumário de contribuições

As crianças infectadas pelo HIV respondem à terapia antirretroviral similarmente quer vivam em lugares com recursos escassos ou em cenário híbrido.

Tanto o estudo de corte transversal realizado com adolescentes infectados pelo HIV de longa duração (transmissão vertical) quanto o estudo de coorte histórico sugerem diferença de gênero na resposta à terapia antirretroviral e manutenção de controle da supressão viral. Esta diferença se mostrou estatisticamente significante tanto para atingir sucesso terapêutico como também para manter este sucesso ao longo do tempo (durabilidade).

Pesquisa futura

A similar resposta terapêutica em crianças e adolescentes vivendo em lugares de recursos escassos ainda requer mais estudos em relação à durabilidade do sucesso terapêutico, efeitos adversos a longo prazo e do papel de comorbidades regionais.

As crianças infectadas pelo HIV atingem a adolescência e a adultícia expostas a longo período de uso de drogas antirretrovirais e a seus efeitos adversos. Vários pontos ainda precisam ser esclarecidos como: qual esquema mais potente (controle da replicação viral), mais duradouro (sem rebote de replicação viral), de melhor aderência e com menos efeitos adversos. Até alcançarmos mais esclarecimentos sobre estes aspectos, este trabalho aponta para problemas de escolaridade que precisam ser melhor avaliados. Qual a razão de problema de escolaridade em adolescentes vivendo com o HIV? Alteração cognitiva por comprometimento do sistema nervoso em tenra idade? Aspectos psicológicos, sociais e/ou culturais, como depressão, revelação do diagnóstico e preconceito, estariam associados à evasão escolar e/ou baixo rendimento escolar? O benefício social (geralmente um salário mínimo) recebido por alguns adolescentes poderia interferir no desempenho ou contribuir para evasão escolar?

A questão de gênero tanto na resposta terapêutica quanto na durabilidade da resposta ao uso de antirretrovirais a longo prazo é particularmente instigante. Isto induz a uma série de especulações e fonte de futuras pesquisas desde aspectos farmacológicos, biológicos, sociais e culturais, envolvendo até as questões relativas à adesão a tratamentos de longa duração.

Recomendações

As conclusões dos estudos compilados nesta tese nos permitem fazer as seguintes recomendações:

1. Incluir em publicações/guias e divulgar entre os profissionais de saúde que lidam com aids pediátrica a efetividade da terapia antirretroviral em crianças e adolescentes e que o critério de sucesso terapêutico é de se atingir controle

duradouro da replicação viral. A publicação do PN-DST/Aids que guia tratamento nesta faixa etária já inclui em 2009 esta recomendação com divulgação em alguns treinamentos macrorregionais.

2. Incluir nos guias de manejo e protocolos de atendimento e acompanhamento de crianças e adolescentes vivendo com aids a necessidade de monitorização periódica da qualidade de vida e do desempenho escolar dos pacientes.

3. Incluir nos guias de manejo e protocolos a informação que a resposta terapêutica pode variar de acordo com o gênero e que medidas para reforçar e assegurar a adesão ao tratamento a longo prazo são necessárias e devem ser aplicadas com envolvimento de toda equipe multiprofissional que lidam com crianças e adolescentes com aids.

11. APÊNDICES

Apêndice 1: Publicação da Carta ao Editor do Jornal de Pediatria

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Conflicts of interest: none. The author has already participated as a researcher in multicenter studies on vaccines financed by Whyeth and Merck Sharp Dohme laboratories, and received grants for lectures on immunizations in symposia and scientific meetings sponsored by Whyeth, Merck, Sanofipasteur and GSK laboratories.

Effectiveness of dual and triple anti-HIV therapy

Dear Editor,

I would like to make some comments about the original article written by Romanelli et al.[1] and about the editorial written by Oleske.[2]

Initially, I want to highlight the importance of the article by Romanelli,[1] which provides health professionals with important information about when to start anti-HIV therapy in children. This and other studies have advocated a change in international guidelines for the treatment of HIV infection in children in the last few years. These guidelines included the initial indication of formal dual therapy, then the restriction on the use of dual therapy (mild cases), and finally, the formal indication of triple therapy.

In regard to the editorial written by Oleske,[2] some explanations and comments are necessary. At the end of the first paragraph, Oleske affirms that the pathogenesis of HIV infection and the general principles of therapy are the same for adults, adolescents, children and infants infected with HIV. However, it has been well established that the dynamics of viral replication and the immunopathogenesis of HIV infection in adults and children have remarkable differences, and some of these differences still have to be clarified.[3,4] And it is the difference in the dynamics of viral replication and pathogenesis of HIV infection in children that determines the different guidelines for antiretroviral therapy in children and adults, especially regarding parameters such as implementation of treatment, treatment success and failure, and peculiarities about immune reconstitution.[5,6]

In the second paragraph, Oleske affirms that the pharmacokinetics of the multiple drugs used in the treatment of HIV infection also accounts for more rapid disease progression in pediatric patients. It is common knowledge that when one refers to progression of HIV infection, one usually describes the natural history of the disease; to be natural, it requires exclusion of antiretroviral therapy. Therefore, this type of inference or casual relationship is not appropriate. I think the article should mention the paucity of pharmacokinetic studies in children, mainly in the first months of life. The available studies usually have a too small sample size and include different age groups.[7,8]

Finally, I would like to remind pediatricians and infectologists who attend to HIV-infected children that the management of pediatric HIV infection in Brazil should follow the Guidelines for Clinical Treatment of HIV Infection in Children, elaborated by the Brazilian National STD/Aids Program of the Brazilian Ministry of Health. These guidelines are updated regularly, and the 2006 version is already available at www.aids.gov.br.

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Apêndice 2: Revisão sistemática sobre o escopo da resposata virológica à terapia antirretroviral em crianças e adolescentes

Tile: Scope of virological response to highly active antiretroviral therapy in HIV-1 infected children: a systematic review

Title page

Short running title: HAART response in HIV infected children

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Abstract

Background: Highly active anti-retroviral therapy (HAART) has been used in HIV-1 infected children and adults, but there is concern that efficacy in pediatric patients is worse than adults.

Objectives: The objective is to determine the rate of the viral suppression in HIV-1 infected children using HAART and to compare it with adults rates.

Methods: The electronic databases searched for the period from 1996 to June 2006 were: Cochrane Library, PubMed, SUMSEARCH, SCIRUS and SCIELO. Experimental and observational studies using HAART in which the main outcome measure was the viral load suppression. Two authors independently assessed studies quality and extracted some data.

Main results: Thirteen studies were selected. The weighted mean of the percentage of viral suppression using 500/400 copies assays was 58.1% (10 treatment groups, 657 subjects; 95% CI, 54.3 to 61.9%) and the ones using 50/40 copies assays was 66.0% (4 treatment groups, 253 subjects; 95% CI, 59.8 to 71.8%) with a median 48 weeks (min. 12, max. 192) of follow-up period. These rates of viral suppression are comparable or sometimes better (50/40 copies assays) than the ones described in therapy-naive adults patients.

Reviewers' conclusions: Children appear to respond to HAART as well as the adults.

Key words: HIV; Therapy; children;

Background

The first antiretroviral drugs to be used in adults and children, were released in late 80s and early 90s [1,2]. Subsequently, the so called highly active antiretroviral therapy (HAART), a combination of at least 3 efficient antiretroviral drugs [3,4] has led to viral suppression, immunological reconstitution, and improvement of the clinical status. As a result, there has been a reduction in the prevalence of the HIV-related conditions, improved quality of life and a marked decline on the AIDS-related mortality rate [5,6].

Most of the studies and clinical trials on the efficacy of HAART have been conducted in adult populations. Few pediatric populations have been examined and considerable uncertainty about efficacy therefore still exists. This fact is expressed in the differences of international guidelines for the treatment of HIV infection. The adult's guidelines mostly agree with the goals of initiating HAART, parameters for the treatment success and virologic considerations for failure. One of the main goals of initiating HAART is to achieve viral suppression expressed as undetectable viral load at 6 months of treatment [7-11]. However, the international guidelines for the use of antiretroviral drugs in infants and children differ when starting therapy, treatment goals and treatment success criteria. PENTA[iii] guidelines stress that a consensus about the definition of virological failure has not been reached yet, but they agree with the adults definition in their aim to reduce viral load to undetectable levels as fast as possible and maintain this status for as long as possible [12]. The Spanish and Brazilian Guidelines advocate that usually is not feasible to achieve viral suppression in an elevated proportion or significant proportion of children. Therefore, the treatment success or the failure should not be based only in virological parameters [13,14]. While US Guidelines emphasize that the initial virological response of infected infants and children may take longer than the ones observed in adults, and the HIV viral suppression may be achieved also less often[15].

[iii] Paediatric European Network for Treatment of AIDS

These differences are based on the fact that infants are infected during a period of immature immune system which allows greater viral replication during acute infection and longer viremia set point after a host immune response takes place. Thus, a viral control with antiretroviral drugs should be harder to achieve and response rates to HAART are inferior in the children to those in the adults [16,17]. However, more recently published data has cast some doubt on these theoretical assertions showing that HAART was able to suppress the viral load below the lower limit of detection in children with a viral decay rate of 2.1 days, similar to adults and irrespective of baseline viral load [18].

The aim of this systematic review was collate evidence about the scope of virological response to highly active antiretroviral therapy in the HIV-1 infected children. The key research question is: Do children respond to HAART with viral suppression as well as the adults?

Objectives

The primary objective of this review is to determine the rate of viral suppression in children using HAART and to compare it with the rate of viral suppression in the adults. We will also describe some features of the study groups such as age, baseline CD4 count and viral load, variety of drug combination and prior use of ARV drugs.

Methods:

We used as reference to perform this review the Cochrane Handbook for Systematic Reviews of Intervention 4.2.5 [19] and the Centre for Reviews and Dissemination's Guidance for those Carrying Out or Commissioning Reviews [20].

Criteria for considering studies for this review

Types of studies

All experimental, quasi-experimental e observational studies using HAART.

Types of participants

Infants, children and adolescents HIV infected by mother-to-child transmission, from birth to 18 years of age. Studies including adolescents HIV infected by sex or blood transmission were excluded since they behave similar to the HIV infected adults. Moreover, adolescents who acquire HIV during adolescence differ in nature history and immunopathogenesis from long-term survival adolescents from mother-to-child transmission.

Types of interventions

The intervention required was the use of antiretroviral therapy including at least 3 drugs from two or three classes of the antiretroviral drugs (NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non- nucleoside reverse transcriptase inhibitor and PI, protease inhibitor).

Types of outcome measures

The outcome measure was the proportion of children with HIV RNA viral load below detection level depending on the type of the assay ($\leq$ 500/400 copies/ml or $\leq$ 50/40 copies/ml) over time (weeks of follow-up).

Search strategy for identification of studies

Firstly, an electronic search was made in distinct databases. Secondly, the reference sections of identified papers were examined for additional publications. Thirdly, we searched our own files.

Electronic searches

Electronic Databases included in the search strategy for the period from 1996 to June 2006 were: Cochrane Library, PubMed, SUMSEARCH, SCIRUS and SCIELO. First, we searched for: “HAART or highly active antiretroviral therapy”, “response or efficacy or effectiveness”, “child or children or pediatric or paediatric”, “viral or virological suppression” and “treatment outcome”. In addition, we further

searched PubMed, MeSH Database, using “HAART” (MeSH) and “treatment outcome” (MeSH) using an age limit to all children (0 < 18 years) and clinical trial. The search was not limited by language.

Other Sources

The primary search was supplemented with an exploration in AIDSSEARCH, AIDSTRIALS, AIDSDRUGS, HIV i-Base Treatment Bulletin, Google, AIDSINFO, (for conferences and international guidelines) with the aim to identify conference abstracts and other reference lists. We hand searched the lists of references of the articles retrieved and other sources [21].

Selection of Studies

All potentially relevant citations and references were identified by two authors using the criteria described above. All titles and abstracts that included clinical trials or cohort studies were retrieved if the main outcome variable was suppression rate of HAART using either ≤ 500/400 or ≤ 50/40 copies/ml. The citations identified had their full text articles selected for potential inclusion.

Data extraction and management

The data extraction and study quality was completed by two independently reviewers (ES and AF). Randomized or open-label clinical trials and cohort studies were assessed by detailed description of the study design and by intention-to-treat analysis in their statistical methods.

Assessment of methodological quality of included studies

We created a table containing the authors’ identification of the citations retrieved, the number of participants, median age, follow up period and measurement on viral load suppression, baseline CD4 count, type of HAART combination, type of viral load level of detection, the year of publication and type of study design. Two reviewers independently evaluate the methodological quality of studies and the disagreements were resolved by discussion of criteria when required. The studies were scrutinized for methodological quality, bias, internal and external validity. The publications were further evaluated if they fit the quality criteria for experimental and observational

studies. To minimize bias and errors we look after studies in which randomization, blinding and intention to treat analysis were used.

Measures of treatment effect

The effect measure were rate of viral suppression achieve as intention-to-treat analysis either $\leq$ 500/400 or $\leq$ 50/40 copies/ml.

Unit of analysis issues

Some studies had multiple treatment groups. We only extracted and included data of the treatment groups using HAART with 2 or more classes of drugs.

Dealing with missing data

Studies without intention-to-analysis or missing statistics details were excluded.

Data synthesis

We synthesize the findings of the multiple studies with the aim to compare the results with overviews and results from reviews of the use of HAART in adults. We tabulated the data from the selected studies and used EpiInfo Version 6.0 and Stata-SE Version 9.2 for the statistics analysis.

Results

Results of the search

The search yielded a total of 979 references; 41 initially met the inclusion criteria. This number was reduced to 13 after further scrutiny (fig 1.) [22-34]. Reasons for study exclusion included: some studies used data from earlier publications on the same participants. A summary of the characteristics of all included studies is showed at Table 1.

All 13 studies yielded different percentages of viral suppression using different detection level assays. Nevertheless, the weighted mean of percentage of viral suppression using 500/400 copies assays was 58.1% (10 treatment groups, 657 subjects;

95% CI, 54.3 to 61.9%) and the ones using 50/40 copies assays was 66.0% (04 treatment groups, 253 subjects; 95% CI, 59.8 to 71.8%) with a median of 48 weeks (min. 12, max. 192) follow-up period.

Description of the studies:

Included Studies

The included studies had the follow profile:

Study design and publication year: from the 13 papers included, 3 (23.1%) papers were open-label prospective cohort studies, 7 (53.8%) were open-label clinical trials and 3 (23.1%) were randomized clinical trials. Six (46.2%) out of 13 studies were published at 2005.

Patient population: a total of 808 patients were included in all studies (median 50, min 10 max 192). The median age when starting HAART, in 10 out of 13 studies, was 6.3 (5,1 to 8,5) years. At baseline, in 8 out of 13 studies, patients median CD4 count was 650 (min. 129 –max. 847) and in 11 out of 13 studies, median viral load was 4.9 (min. 4- max. 5,3).

Interventions: Treatment (HAART) consisted of 3 or 4 drugs of 2 or 3 classes and the median follow-up period was 48 weeks (min 12, max 192). According to a pre-exposure to antiretroviral drugs: 6 (46.2%) studies all patients had been exposured to ARV drugs, 4 (30.8%) studies had mixed naïve and ARV experienced patients and 3 (23.1%) studies had only naïve patients.

Laboratory data: According to the lower limit of detection of plasma HIV-1 RNA load assays used, 7 (53.8%) studies used 500 or 400 copies assays, 4 (30.8%) studies used 500 or 400 and 50 or 40 and 2 (15.4 %) studies used only 50 copies assay.

Excluded Studies

The characteristics of the excluded studies were: retrospective design, compassionate access and/or ARV multi-experimented patients, cross-over studies, and on treatment analysis.

Discussion

The results of this systematic review suggest that HIV infected children respond to HAART as well as the adults. This notwithstanding, the dynamics of viral replication and the immune pathogenesis of the HIV infection in adults and children have remarkable differences, and some of these differences still have to be elucidated [35].

The rates of viral suppression in HIV-infected children using HAART in this systematic review offer a distinctive chance to compare with the rates in HIV-infected adults. Furthermore, these results present us a chance to answer the question: Do children respond to HAART with viral suppression as well as the adults?

Bartlett *et al* in 2001 published one of the most importance overview about the effectiveness of HAART in HIV-1 infected therapy-naïve adults [36]. In this overview, the overall percentage of patients having plasma HIV RNA $\leq$ 400 copies/ml at week 48 was 55% (24 treatment groups, 2,561 subjects; 95% CI, 51 to 58) and for patients having plasma HIV RNA $\leq$ 50 copies/ml at week 48 was 47% (22 treatment groups, 2,331 subjects; 95% CI, 43 to 51). In comparison with the results of our review, there is no difference to HIV RNA $\leq$ 400 copies/ml group ($p = 0.17$). On the other hand, for the HIV RNA $\leq$ 50 copies/ml group, our review rate of suppression of 66 % was greater ($p < 0.000001$).

In 2006, Bartlett *et al* published an updated and expanded overview [37]. In this updated review of therapy-naïve adults, the overall percentage of patients having plasma HIV RNA $\leq$ 400 copies/ml at week 48 was 66% (66 treatment groups, 11,937 subjects; 95% CI, 64 to 68) and for patients having plasma HIV RNA $\leq$ 50 copies/ml at week 48 was 55% (79 treatment groups, 13,558 subjects; 95% CI, 54 to 57). In comparison with the results of our review, they showed a greater rate of suppression to HIV RNA $\leq$ 400 copies/ml group ($p = 0.000026$)). However, for the HIV RNA $\leq$ 50 copies/ml group, our review rate of suppression of 66 % was greater ($p = 0.0005$).

Although our results show similarities in the rate of suppression or even better results compared with the adults, we must stress that our review comprised ARV naïve and non-naïve subjects while Bartlett's overviews comprised only naïve patients, who

theoretically should respond better to HAART. Nevertheless, the trend of the rates of suppression is increasing over time in children and adults [27, 38].

Some limitations identified of this review. There is still a limited number of articles studying the efficacy of HAART on children. Furthermore, some of the existing studies consist of an undersized number of subjects and some including a wide age group.

Reviewers' conclusions

This systematic review was conducted as an effort to solve conflicting evidence about the scope of the virologic response to highly active antiretroviral therapy in HIV-1 infected children. We think we answered the question: Do children respond to HAART as well as the adults? This review answer is yes, but improvements in the HIV suppression rates over time are needed in children and adults. Moreover, we suggest that multicenter efficacy studies are needed to further explore the subject of HAART efficacy in childhood.

Acknowledgements

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Potential conflict of interest

There is no conflict of interest.

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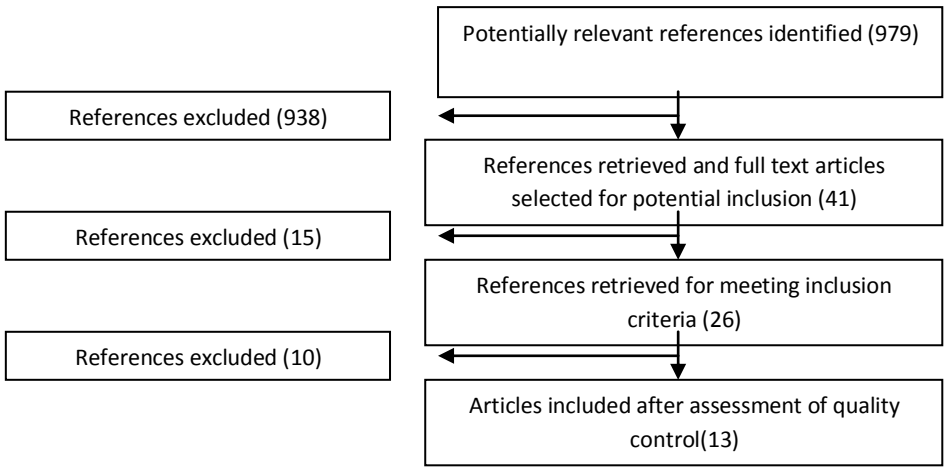

Figure 1 - Course of studies through the review

Table 1. Characteristics of included studies[2] (to be continued)

Study	Design	Patients (n)	Median (mean*) age	Median (mean*) baseline CD4+ count (/mm^3 or %)	Median (mean*) baseline viral load (Log_{10} Copies/ml)	Treatment (HAART)	Duration of follow-up (weeks)	Assays cut-off (cp/ml)	ITT (%)	Previous ART treatment	Publication's year
Fraaij et al [22]	Open label prospective cohort study	31	5.1 yr (0.2-16.4)	480(0-3580)	4.94 (2.86-6.34)	2 NRTIs + IDV or NFV	192	< 500	65	Mixed	2005
								< 50	61		
Chadwick et al[23]	Open label clinical trial	50	4wks-24mos			ZDV+3TC+RTV	16	< 400	72	Mixed	2005
		A: 17	3.2mos (1.1-24)	2,399 (769-5,233)	5.3 (2.6-6.8)		104		36	(PI naïve)	
		B: 33	3.6mos (1.2-23.3)	1,579 (77-3,740)	5.5 (3.2-6.5)						
Luzuriaga et al[24]	Open label multicenter trial	52	2.0mos (0.5-3)	36% (14-63)	5.3 (3.3-6.4)	ZDV+3TC+NVP	48	< 400	24-29	All	2004
		(N=18)				ZDV+3TC+NVP+ABC	200		41-29	(PI naïve)	
						d4T+3TC+NVP+NFV			83 –72		
Starr et al[25]	Open label clinical trial	57	8 yr (3.8-16.8)	699 (4-2,616)	4.0 (2.6-5.7)	1 or 2 NRTI + EFV+ NFV	48	< 400	76	All	1999
								<50	63		
Krogstad et al[26]	Multicenter randomized clinical trial	192	6.2yr (4mos-17yr)	696	4.39	d4T+NVP+RTV	48	< 400	41	Mixed	2002
						d4T+3TC+NFV			30	(PI and NNRTI naïve)	
						d4T+NVP+NFV			42		
						d4T+3TC+NVP+NFV			52		
									Mean: 41,25		
Funk et al[27]	Open label clinical trial	10	5.8	378	5.5	2 NRTI + EFV	24	< 50	80	Naïve	2005
Funk et al[28]	Open label prospective study	16	77mos (14-152)	656 (15-2,250)	5.3 (4.56-6.70)	ZDV+3TC+NFV	12	< 500	69	Naïve	1999
						d4T+ddI+NFV		< 50	44		
van Rossum et al[29]	Open label prospective multicenter trial	32	5,4 yr (0,4-16,4)	Clinical stage (CDC classification)	5.13 (3.43-5.88)	ZDV+3TC+IDV or NFV	96	< 500	69	All	2002
								< 40	50	(PI naïve)	
Saez-Llorens et al[30]	Open label clinical trial	100	5.3y* (6mos -12.6yr)	847*	4.7*	A: d4T+3TC + LPV/r	48	<400	79	Mixed	2003
			A=ARV naïve	A: 920* (40-3.340)	A:4.9*	B: NVP + 1 or 2 NRTI + LPV/r			A: 84		
				B: 773* (15-2.595)	B: 4.5*				B: 75		
			4.8y* (6mos-10.2yr)								
			B=ARV-exp								
			5.7y* (8mos-12.6yr)								
Ananworanich et al[31]	Open label prospective trial	20	8.5yr (6.9-9.9)	129 (35-243)	4.9(4.5-5.4)	SQV+LPV/R alone or with 3TC	24	< 400	80	All	2005
Puthanakit et al[32]	Open label clinical trial	107	7.7 yr*(2.1-13,8)	3% (1-9)	5,4* (4.9-5.9)	d4T+3TC+NVP or EFV	72	<50	76	Naïve	2005
				< 6 yr - 97 (44-3-7)							
				> 6 yr – 46 (30-71)							

Table 1. Characteristics of included studies[2] (conclusion)

Study	Design	Patients (n)	Median (mean*) age	Median (mean*) baseline CD4+ count (/mm^3 or %)	Median (mean*) baseline viral load (Log_{10} Copies/ml)	Treatment (HAART)	Duration of follow-up (weeks)	Assays cut-off (cp/ml)	ITT (%)	Previous ART treatment	Publication's year
Nachman et al[33]	Randomized clinical trial	100	7.4yr	644	4.41	AZT+3TC+RTV	48	< 400	42	All	2000
King et al[34]	Randomized clinical trial	41	6.4yr				48	< 400	MEAN:=46,5	All	2005
		A: 21	5.3yr (1.3-11.2)	751 (205-1,395)	4.42 (3,49-5.86)	ddI+NFV+RTV			65	(PI naïve)	
		B: 20	7.0yr (0,4-20.8)	610 9152-3,571)	4.45 (3.07-5.51)	d4T+NFV+NVP			28		

[2] Numbers and association of drugs in bold were used for analysis. ART, antiretroviral drugs; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; IDV, PI, protease inhibitors; indinavir; NFV, nelfinavir; ZDV, zidovudine; 3TC, lamivudine; RTV, ritonavir; NVP, nevirapine; ABC, abacavir; d4T, stavudine; EFV, efavirenz; ddI, didanosine; LPV/r, lopinavir/ritonavir, SQV, saquinavir; ITT; intention to treat analysis.

12. ANEXOS

Anexo 1: Comprovação de Submissão de Estudo de Coorte Histórico.

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