Síndrome metabólico: diagnóstico y tratamiento

María Espiau Hospital Vall d'Hebron, Barcelona



CLINICAL SCIENCE

Mortality in the Highly Active Antiretroviral Therapy Era Changing Causes of Death and Disease in the HIV Outpatient Study

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Conclusions: Although overall death rates remained low through 2004, the proportion of deaths attributable to non-AIDS diseases increased and prominently included hepatic, cardiovascular, and pulmonary diseases, as well as non-AIDS malignancies. Longer time spent receiving HAART and higher CD4 cell counts at HAART initiation were associated with death from non-AIDS causes. CD4 cell count at time of death increased over time.

Causes o with Ant Analysis

The Antiretroviral T

Table 3. Frequencies of Specific Causes of Death in the 1597 Patients Who Died, with Crude Incidence Rates per 1000 Person-Years of Follow-up

Cause of death	No (%) of patients ^a $(n = 1597)$	Incidence rate (95% CI) per 1000 years
AIDS		
All	792 (49.6)	5.12 (4.78-5.49)
Nonspecified AIDS	190 (11.9)	1.23 (1.07-1.42)
AIDS infection	366 (22.9)	2.37 (2.14-2.62)
AIDS malignancy	236 (14.8)	1.52 (1.34-1.73)
Non-AIDS malignancy	189 (11.8)	1.22 (1.06-1.41)
Non-AIDS infection CVD ^b	131 (8.2)	0.85 (0.71–1.01)
All	126 (7.9)	0.81 (0.68-0.97)
MI/IHD	51 (3.2)	0.33 (0.25-0.43)
Stroke	23 (1.4)	0.15 (0.10-0.22)
Other heart disease	52 (3.3)	0.34 (0.26-0.44)
Violence ^c		
All	124 (7.8)	0.80 (0.67-0.96)
Suicide	48 (3.0)	0.31 (0.23-0.41)
Substance abuse	42 (2.6)	0.41 (0.32-0.52)
Other violent death	34 (2.1)	0.22 (0.16-0.31)
Liver related		
All	113 (7.1)	0.73 (0.61-0.88)
Hepatitis related	63 (3.9)	0.41 (0.32-0.52)
Other liver related	50 (3.1)	0.32 (0.25-0.43)
Respiratory disease	25 (1.6)	0.16 (0.11-0.24)
Renal failure	24 (1.5)	0.16 (0.10-0.23)
Other causes with n < 20	73 (4.6)	0.47 (0.38-0.59)

NOTE. CI, confidence interval; CVD, cardiovascular disease; MI/IHD, myocardial infarction/ ischemic heart disease.

Freated borative

a 39,272 patients with 154,667 years of follow-up.

b CVD includes MI/IHD, stroke, heart failure/unspecified, and other heart disease.

Oviolence includes homicide, accident, suicide, and substance abuse, as well as ill-defined violent deaths.

Antiretroviral therapy, fat redistribution and hyperlipidaemia in HIV-infected children in Europe

European Paediatric Lipodystrophy Group*

Objectives: To estimate prevalence of body fat redistribution and dyslipidaemia in HIV-infected children and to assess associated risk factors, ultimately to inform the definition of lipodystrophy in children.

Design: Cross-sectional observational study.

Methods: During a 2–3 month period, 477 HIV-infected children aged \geq 3 years (median 9.78; range, 3–18) in 30 paediatric HIV clinics were assessed at their first visit. Sociodemographic, clinical and immunological data were recorded and the presence or absence of clinical signs of fat redistribution (peripheral lipoatrophy and central lipohypertrophy) determined according to an agreed protocol. Laboratory indicators of lipid/glucose metabolism were recorded for all children in 18 centres.

Results: Prevalence was 26.0% [95% confidence interval (CI), 22.1–30.2] for any fat redistribution, 8.81% (95% CI, 6.42–11.7) for central lipohypertrophy, 7.55% (95% CI, 5.34–10.3) for peripheral lipoatrophy and 9.64% (95% CI, 7.15–12.7) for the combined subtype (more than one sign of each). Independent predictors of fat redistribution included Centers for Disease Control and Prevention class C disease, female gender, ever used versus never use of protease inhibitors and of stavudine. Increasing time since initiation of antiretroviral therapy was associated with increased severity of fat redistribution. In the metabolic assessment subgroup, 27% (95% CI, 21.6–32.7) of children had hypercholesterolaemia and 21% (95% CI, 16.4–26.6) hypertriglyceridaemia; however, significantly more children had fat redistribution in this subgroup than overall (31%).

Conclusions: Approximately a quarter of children and adolescents could be taken to have signs of lipodystrophy, with clinical presentation and risk factors similar to those described in adults.

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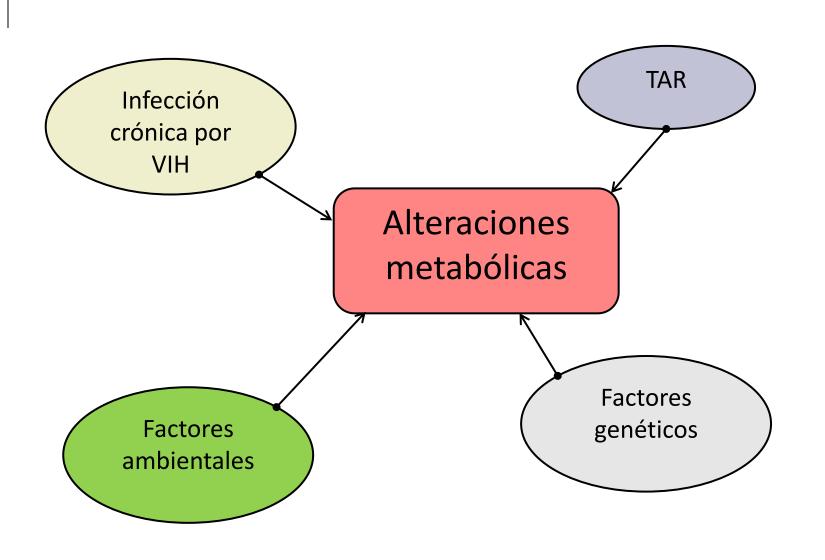
Metabolic disorders in vertically HIV-infected children: future adults at risk for cardiovascular disease

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³ Pediatric Infectious Diseases Unit, Department of Pediatrics, Hospital Universitari Sant Joan de Déu – Universitat de Barcelona, Esplugues de Llobregat, Spain Results: We included 157 patients [median age 13 years, interquartile range (IQR) 10–16]. Median duration of antiretroviral therapy was 10.2 years (IQR 5.0–13.0). Almost 20% of patients had insulin resistance and this was associated with hepatitis C co-infection, current use of stavudine (d4T) and hypertriglyceridemia. Hypercholesterolemia and hypertriglyceridemia were found in 23.9% and 24.8% of patients and were associated with current use of protease inhibitors (p=0.042 and p=0.022, respectively). Abnormal fat distribution was observed in 63 patients (40.5%): lipoatrophy in 32 (20.4%), lipohypertrophy in eight (5.1%) and a mixed pattern in 23 patients (14.6%), and it was significantly associated with previous exposure to stavudine (p<0.001).



- VIH... ↑ TG, ↓ HDLc, ↓ LDLc
- TARGA... ↑ LDLc
- EFV, NVP... ↑ HDLc
- IP potenciados... 个 TG
- VIH, d4T, AZT, NFV... lipoatrofia
- VIH, IP, análogos de timidina... alt. glucosa

Síndrome metabólico (SMet)

= obesidad abdominal

 HTA

dislipemia

hiperglicemia o resistencia insulínica

= factor de riesgo independiente de enfermedad CV (R ictus/IAM x 2-3) y DM (R x 5)

Criterios de SMet en Pediatría

Pediatric Diabetes 2007: 8: 299–306 All rights reserved © 2007 The Authors Journal compilation © 2007 Blackwell Munksgaard

Pediatric Diabetes

Review Article

The metabolic syndrome in children and adolescents – an IDF consensus report

Zimmet P, Alberti K George MM, Kaufman F, Tajima N, Silink M, Arslanian S, Wong G, Bennett P, Shaw J, Caprio S; IDF Consensus Group. The metabolic syndrome in children and adolescents – an IDF consensus report.

Pediatric Diabetes 2007: 8: 299-306.

Criterios de SMet en Pediatría

Grupo de edad	Obesidad (perímetro abdominal)	Triglicéridos	Colesterol HDL	Tensión arterial	Glucosa
6-10 años	≥ percentil 90	No se puede diagnosticar SMet, pero se deberá repetir las mediciones en caso de historia familiar de DM tipo 2, dislipemia, síndrome metabólico, enfermedad cardiovascular, hipertensión u obesidad			
10-16 años	≥ percentil 90 (o punto de corte de adultos si es menor)	≥ 150 mg/dl	< 40 mg/dl	TAS ≥ 130 mmHg y/o TAD ≥ 85 mmHg	≥ 100 mg/dl Recomendar TTOG si >100 mg/dl.
> 16 años	Equiparable al diagnóstico de SMet en el adulto				

≥ 2

Detección y seguimiento

Category	Frequency	Measures	Triggers and Additional Considerations
Anthropometry	6 months	Height, weight, BMI, skinfolds (tricep, bicep, suprailiac, subscapular), waist and hip circumference	 Weight Z score ≤-2 or ≥2 Height Z score <-2 BMI Z score <-2 or >2 at risk for overweight or overweight
Diet	6 months	24-hour dietary recall, 3-day food record, or food frequency questionnaire	• See Table II
Body composition	Annual	Bioelectric impedance analysis; dual energy x-ray absorptiometry	
Lipids	3-6 months	Lipid blood panels	• AHA guidelines ⁵⁴
Glucose/insulin	3–6 months	Baseline fasting glucose and fasting insulin with repeat assessments for comparison	 Glucose >100 mg/L Insulin >2.5 (Tanner I) Insulin >4 (Tanner II–V)
Blood pressure	3 months	If first value is abnormal, would perform additional 2 measures, separated by 5-minute intervals	 Monitor readings above acceptable range⁵⁵ If pressure is abnormal, repeat in 1 month; consider intervention

Recomendaciones.

- Las mediciones de lactato en el paciente asintomático no están indicadas. Sólo están indicadas, junto a bicarbonato, en pacientes con sintomatología compatible con acidosis láctica (nivel de evidencia B).
- En el manejo clínico diario del síndrome de redistribución grasa, se aconseja utilizar los marcadores antropométricos junto con la valoración subjetiva del paciente, los tutores y el mismo observador médico (nivel de evidencia B)
- La DEXA es la técnica de elección para el diagnóstico y evolución del síndrome de redistribución grasa en niños, aconsejándose realizar una exploración cada dos años si está disponible (nivel de evidencia B).
- Debe realizarse la determinación rutinaria de colesterol (total, LDL y HDL) y triglicéridos en ayunas cada 3 meses, sobre todo en aquellos niños con TAR (nivel de evidencia B).
- Debe realizarse la determinación rutinaria de la glucemia en ayunas cada 3 meses, sobre todo en aquellos niños con TAR. Valores anormales (glucemia > 110 mg/dl) en dos ocasiones indican la necesidad de una prueba de sobrecarga oral de glucosa (nivel de evidencia B)
- En caso de estar disponible, podría ser útil la realización de eco-doppler de carótida interna en pacientes con factores de riesgo cardiovascular (hiperlipidemia, intolerancia hidrocarbonada, lipodistrofia, tratamiento prolongado con inhibidores de proteasa) para identificación de engrosamiento de la capa íntima arterial (nivel de evidencia B)

Prevención

- Estilo de vida
 - Dieta adecuada, asegurar nutrición
 - Evitar el sobrepeso
 - Evitar hábitos tóxicos
 - Ejercicio físico regular
- Elección de fármacos según perfil de seguridad
- Inicio precoz del tratamiento

Nutrient	Recommended Intake	Additional Comments
Total calories (energy)	Based on child's growth pattern, usual intake, diet history, and exercise pattern. Overall nutritional adequacy should be achieved by eating a wide variety of foods.	If intakes of fat, along with carbohydrate and protein, are inadequate to meet energy needs, the child will be in negative energy balance. Intakes greater than recommended may result in increased cardiometabolic risk and obesity.
Carbohydrate	About 55% of total calories. No more than 10% of carbohydrates should be from sucrose or other refined carbohydrates.	Should derive predominantly from foods rich in complex carbohydrates including grains (especially whole grains), fruits, and vegetables.
Fibers	A reasonable intake is 0.5 g/kg/d to a maximum of 35 g daily.	Consider increased viscous soluble fiber (10–25 g/d); dietary sources: oatmeal, legumes, and some fruits and vegetables with pectin.
Fat	Total fat no more than 30% of total calories and no less than 20% of total calories. Saturated fatty acids <10% of total calories (<7% for therapeutic approach). Trans fatty acids as low as possible (limit processed foods, hard fats, and hard margarine as a practical way to limit intake of saturated and trans fatty acids). Cholesterol <300 mg/d (<200 mg/d for therapeutic approach). Polyunsaturated fatty acids (PUFA), up to 10%. • n-3 PUFA: 1%–2%; n-6 PUFA: 4%–13% • n-6:n-3 ratio = 5:1 to 10:1 Monounsaturated fatty acid 10%–15%.	 Provide anticipatory guidance regarding the importance of a low-fat, low-saturated fat, low-cholesterol diet for all otherwise healthy HIV-infected patients older than 2 years and their families. No restriction of fat or cholesterol is recommended for children aged <2 years when rapid growth and development require high energy intakes. There are indications that variations of the ratio of n-6 to n-3 modulate allergy, inflammation, clotting, and vascular responses.

Protein	About 15% to 20% of total calories. DRI, estimated average intake based on age and body weight.	The variation in requirements is based on the variation in both maintenance needs and the rate of protein deposition (protein for growth).	
Calcium	Based on DRI for age (1997). Currently, evidence is inadequate to alter the dietary recommendations for children living with a chronic illness (eg, HIV) or those taking medications that alter bone metabolism. However, an effort should be made to achieve at least the recommended intake levels. The provision of adequate vitamin D also may be important for children with chronic illnesses.	The largest source of dietary calcium for most persons is milk and other dairy products. Knowledge of dietary calcium sources is a first step toward increasing the intake of calcium-rich foods.	
Plant stanols/sterols	2 g/d. Plant sterols safely and effectively reduce serum cholesterol concentrations by inhibiting cholesterol absorption.	Dietary consumption of plant stanols/sterols can be obtained from commercially available products containing plant sterols/stanols (eg, margarine, juices).	
Vitamin D	Based on DRI for age (1997). The Committee on Nutrition of the AAP recommends a supplement of 200 IU/d for children and adolescents who do not get regular sunlight exposure, do not ingest at least 500 mL/d of vitamin D-fortified milk, or do not take a daily multivitamin supplement containing at least 200 IU of vitamin D.	Dietary sources include fortified foods (eg, milk and breakfast cereals).	
Antioxidant and micronutrient supplements	Multivitamin use at DRI levels can be an easy and inexpensive adjunctive therapy to decrease the side effects of HAART therapy and to improve clinical outcomes in HIV-infected children.	Intervention studies on single antioxidant vitamins (A, C, E, and β-carotene) have been few and have shown mixed beneficial effects on decreasing oxidative stress.	
Abbreviations: AAP, American Academy of Pediatrics ⁴⁶ ; DRI, dietary reference intake ⁴⁷ ; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus.			

Tabla V. Recomendaciones de inicio del TAR

EDAD	CRITERIO	TRATAR
0-11 meses	Clínico Inmunológico Virológico	TODOS TODOS TODOS
12-35 meses	Clínico Inmunológico	Estadio B ó C* CD4 <25% ó < 1000/mm³
36-59 meses	Clínico	Estadio B ó C
> 5 años	Inmunológico Clínico	CD4 <25% ó < 750/mm³ Estadio B ó C*
- 5 anos	Inmunológico	CD4 <350-500*

^{*} Categoría B: En un único episodio de infección bacteriana grave la consideración de inicio debería hacerse por parámetros inmunológicos

En pacientes con una carga viral superior a 100.000 copias/ml se debería considerar el tratamiento, y en caso de no comenzar se recomienda un seguimiento clínico y analítico muy estrecho (**B-III**).

^{*}Las guías del PENTA establecen el inicio del TAR cuando los CD4 están por debajo de 350 cels/mm3 en niños mayores de 5 años.

Tratamiento

Cambios en el estilo de vida

Modificaciones del tratamiento ARV

3. Tratamientos farmacológicos específicos

4. Enfoque multidisciplinar

Strategy	Effect	Comments
Lipoatrophy		
Switching antiretroviral therapy	Modest effect	Switching from stavudine or zidovudine to abacavir or tenfovir disoproxil fumarate; best available strategy for lipoatrophy
Thiazolidinediones	Modest effect	Effect not clinically significant; availability of rosiglitazone limited due to increased risk of cardiovascular disease; pioglitazone associated with decreased levels of triglycerides, increased levels of HDL cholesterol
Pravastatin	No effect	NA
Uridine	No effect	NA
Facial fillers	Clinically significant effect	Potential adverse effects include fat hypertophy with autotransplatation, skin nodules with resorbable fillers and local infections with permanent fillers
Leptin	Unclear	No effect on peripheral adipose tissue, but may improve insulin resistance and dyslipidemia
Lipohypertrophy		
Switching antiretroviral therapy	No effect	Overall, no benefit except for switching from lopinavir plus ritonavir to atazanavir plus ritonavir in one small study
Lifestyle changes	Modest effect	NA
Metformin	Modest effect	May worsen lipoatrophy
Growth hormone	Clinically significant effect	Rejected by FDA because of safety concerns
Tesamorelin	Clinically significant effect	FDA-approved in 2010; long-term benefits and risks unclear
Liposuction (dorsocervical fat pad)	Clinically significant effect	Can reaccumulate

Brown, T. T. & Glesby, M. J. Nat. Rev. Endocrinol. advance online publication 20 September 2011

Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents : A Scientific Statement From the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, With the Council on Cardiovascular Nursing

Brian W. McCrindle, Elaine M. Urbina, Barbara A. Dennison, Marc S. Jacobson, Julia Steinberger, Albert P. Rocchini, Laura L. Hayman and Stephen R. Daniels

Circulation. 2007;115:1948-1967; originally published online March 21, 2007;

Twenty percent to 50% of HIV-infected children treated with highly active antiretroviral therapy that includes protease inhibitors have been shown to develop lipoprotein abnormalities, most commonly increased total and LDL cholesterol levels. In adults, lipoprotein abnormalities have been shown to be associated with an increased risk of cardiovascular disease. Currently, other than dietary treatment no consensus exists as to what lipoprotein levels should be treated in the pediatric patient in whom treatment with protease inhibitors is necessary. 88 One should be cautious in prescribing statins, especially at higher doses, in this group of patients because of the increased risk of myositis/myolysis when statins are given in conjunction with protease inhibitors or azole antifungal drugs.

Condition	Treatment	Considerations
Diabetes mellitus	Biguanides (metformin)	 Effective first-line therapy Approved for use in children Adverse effects include abdominal pain, nausea, vomiting, and increased risk of lactic acidosis
	Sulfonylureas (acetohexamide, tolazamide, glyburide, glimepiride)	 Used in concert with first-line therapies Not currently approved in children (clinical trials in process) Adverse effects include weight gain, hypoglycemia, nausea, vomiting, and skin rashes
	Other medications (meglitinides, thiazolidinediones, α-glucosidase inhibitors)	 Not approved in children Useful in concert with monotherapy Various side effects including flatulence, weight gain, fluid retention, and short duration of action
	Insulin	 Recommended only after other methods fail 0.5–1.0 U/kg body weight per day Dose adjustments are necessary until diabetes is controlled Must be referred to pediatric diabetes specialist
Dyslipidemia	HMG-CoA reductase inhibitors (statins)	 Adverse interaction with protease inhibitors Increased risk of hepatoxicity Preferably used in older children (≥13 y)
	Bile acid-binding resins (cholesterolymine)	 Only drug approved for children <8 y Effective for lowering total cholesterol Increased risk of hypertriglyceridemia
	Other medications	Not approved in children
	(niacin, fibrates)	Most effective as combination therapy
	Dietary supplements	 Fiber, omega-3 fatty acids, and sterol/stanol margarines

TABLA 1. Indicaciones, efectos secundarios y contraindicaciones de fármacos hipolipidemiantes usados en pacientes con infección por VIH

	<u> </u>		
Fármacos	Indicación	Efectos secundarios	Comentarios
Estatinas	> Efecto sobre COL Pravastatina: > 8 años, dosis: 20-40 mg/día Atorvastatina: > 10 años, dosis: 10-20 mg/día	Rabdomiólisis (se agrava con uso concomitante de fibratos)	Lovastatina y simvastatina no deben usarse con IP NFV y EFV pueden disminuir la concentración de pravastatina hasta el 40%
Fibratos	> Efecto sobre TG Poca experiencia en pediatría (sólo TG > 500 mg/dl) Dosis: 150-300 mg/12 h	Mositis Toxicidad medular	Evitar combinación estatinas + fibratos
Ezetimiba	Similar efecto COL/TG Seguro y eficaz en > 10 años Dosis: 10 mg/día	Escasos y leves Síntomas gastrointestinales Mialgias	Estudios en adultos con ezetimiba + estatinas y ezetimiba + fibratos

COL: colesterol; EFV: efavirenz; IP: inhibidores de la proteasa; NFV: nelfinavir; TG: triglicéridos.

An Pediatr (Barc). 2008;68(5):425-31

SÍNDROME METABÓLICO EN NIÑOS Y ADOLESCENTES QUE VIVEN CON EL VIH: RIESGO DE ENFERMEDAD CARDIOVASCULAR EN LA EDAD ADULTA. ESTUDIO EN UNA COHORTE NACIONAL DE PACIENTES VIH PEDIÁTRICOS (CORISPe).

Coordinadores:

Pere Soler-Palacín (Hospital Universitari Vall d'Hebron) Marisa Navarro (Hospital Universitario Gregorio Marañón)

Objetivos

1. Principales:

- Conocer la prevalencia de SMet en la población pediátrica infectada por VIH en nuestro país.
- Reconocer los factores de riesgo de SMet asociados a la propia infección y al TARGA potencialmente prevenibles.

2. Secundarios:

- Describir otros factores de riesgo independientes del VIH y su tratamiento en esta población.
- Proponer una guía de seguimiento de estos pacientes para la prevención de la enfermedad cardiovascular.

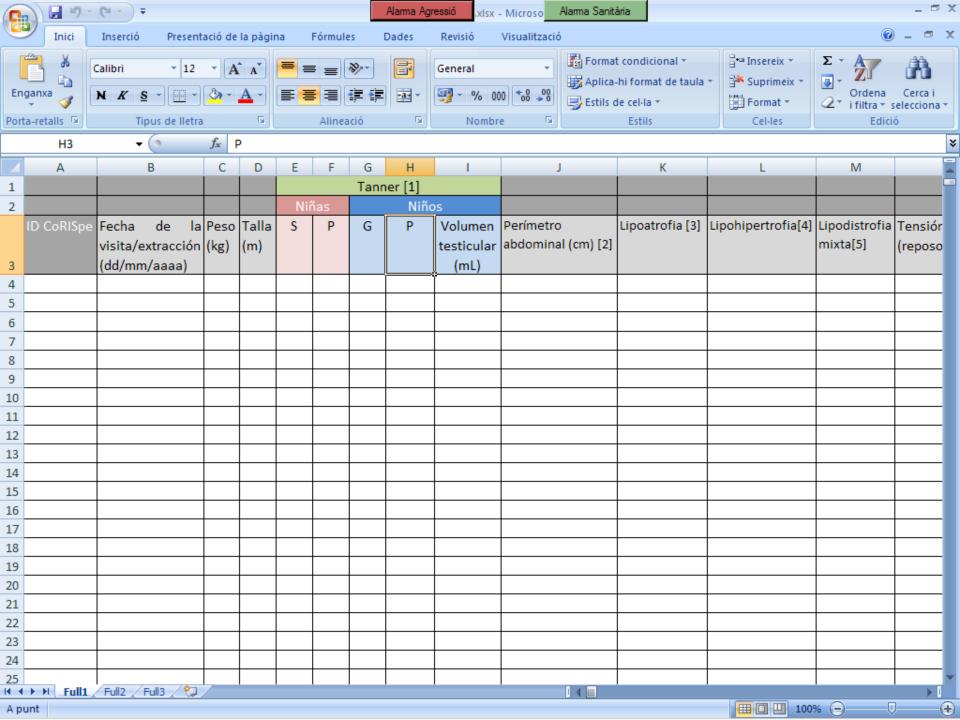
Metodología

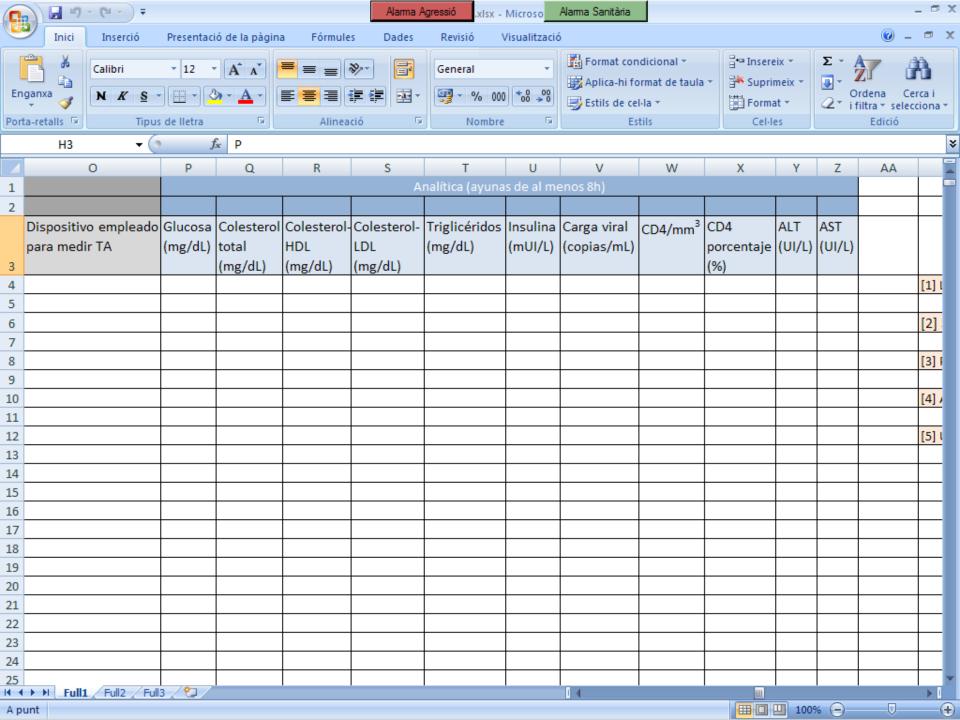
- Estudio prospectivo transversal en todos los pacientes pediátricos infectados por el VIH de la CoRISpe.
- Análisis de datos demográficos, clínicos, inmunológicos, virológicos y tratamiento antirretroviral.

Determinación de:

- Peso, talla y Tanner
- TA en reposo.
- Perímetro abdominal.
- ¿Lipodistrofia?
- Perfil lipídico.
- Glucemia, insulinemia y HOMA-IR
- CV y CD4
- AST/ALT







Plan de trabajo

- Primer trimestre de 2012: redacción del documento y remisión al CEIC del Hospital Coordinador. Posterior envío de copia del documento de aprobación – si se diera- al resto de centros que incluyan pacientes.
- Segundo y tercer trimestre de 2012: extracción de las muestras, medición de tensión arterial y perímetro abdominal y remisión de los resultados obtenidos al centro coordinador.
- Último trimestre de 2012: evaluación, discusión y presentación de los resultados obtenidos.

Pacientes - hospitales

- Nodo 1
 - H. Clínico de Zaragoza 10 pacientes
 - H. San Juan de Alicante 17 pacientes
- Nodo 2
 - HUVH 16 pacientes
 - H. Joan XXIII 2 pacientes
 - H. Josep Trueta 2 pacientes

47 pacientes

Relevancia

Diagnóstico precoz de SMet.

Instauración de medidas de prevención y tratamiento.

Información a los infectólogos de adultos que reciben a estos pacientes de su realidad CV.

Conclusiones

- Prevalencia alteraciones metabólicas (¿y Smet?) en niños que viven con el VIH
 - → efectos a largo plazo

Prevención!!!

Seguimiento y tratamiento



¡MUCHAS GRACIAS POR VUESTRA ATENCIÓN!



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