総　　説

HTLV-1 母子感染予防での小児保健関係者の役割

根路銘安仁

はじめに

HTLV-1 の感染と起因する疾患群への対策に総合的に取り組むため，2010 年 9 月に内閣総理大臣の指示により「HTLV-1 特命チーム」が設けられ，「HTLV-1 総合対策」が開始された。小児保健分野では，母子感染予防のために全国で妊婦の抗 HTLV-1 抗体検査が全例公費負担で実施されるようになった。それに伴い，医師向け手引き[1]および保健指導マニュアル[2]が作成され，2017 年に厚生労働研究事業（代表　板橋家頭夫）により「HTLV-1 母子感染予防対策マニュアル」[3]が作成された。

本年，前研究班でのコホート研究で短期母乳栄養法と完全人工栄養法を選択した場合に母子感染率に有意な差はなかったエビデンス[4,5]をうけて厚生労働科学研究（代表者　内丸薫）が 2022 年にマニュアル改訂を行った[6]。今回の改訂でも人工栄養が最も確実な方法である。一方，短期母乳栄養は「母親が母乳を与えることを強く希望する場合」に限り選択肢として考慮することであったが，90 日未満で完全人工栄養に移行する支援を行うことで完全人工栄養とともに選択肢として含められることになった。短期母乳を選択するには支援する体制を整備することが必須である。短期母乳選択者への支援において小児保健関係者も産科医療施設，小児医療施設，行政機関に所属しており，連携するため互いの支援内容の理解を深める必要がある。今回，マニュアル改訂を機会に HTLV-1 母子感染予防について概説する。

Ⅰ．我が国の HTLV-1 母子感染対策のあゆみ

1．HTLV-1 と母子感染対策の歴史

1977 年に高月清らにより成人 T 細胞白血病（Adult T cell leukemia：ATL，以後 ATL）が報告された[7]。1981 年には日昭賴夫が ATL と関連するウイルスとして HTLV-1 を報告した[8]。1985 年に日野茂男らが母乳を介した感染の成立を証明し，母子感染の対策のきっかけを作った[9]。

HTLV-1 流行地域で，それぞれ率先して研究対策が行われ成果を上げてきた。長崎県では 1987 年には ATL ウイルス母子感染防止研究協力事業（ATL Prevention Program Nagasaki：APP）を開始し現在まで継続している[10]。鹿児島県でも 1985 年から鹿児島大学と共同研究を行い，短期母乳栄養法を確立し，1997 年から鹿児島 ATL 制圧 10 ヵ年計画を実施[11]して完全人工栄養法と短期母乳栄養法から選択することを臨床で確立した。しかし，1991 年に厚生省心身障害研究重松班でキャリア率の高い地域でのみの対策で十分であり，全国一律の検査や対策は必要ないと提言され[12]，全国的な対策はとられることは無かった。

その後，20 年ほど全国的な研究対策は低迷したが，2009 年厚生労働科学研究山口班報告で，HTLV-1 キャリア（以降キャリア）が全国に拡散している事が明ら

The Role of Child Health Personnel in the Prevention of HTLV-1 Mother-to-child Transmission
Yasuhiro Nerome
鹿児島大学医学部保健学科看護学専攻成育看護学講座

かとなり[13]，研究者や患者団体等の働き掛けもあって，「HTLV-1 総合対策」が開始され，全国で妊婦の抗 HTLV-1 抗体検査が全例公費負担で実施されるようになった。

2. HTLV-1 に関連する疾病

HTLV-1 は，関連する疾患は多くあるが，主なものとして ATL，HTLV-1 関連脊髄症（HTLV-1-associated myelopathy：HAM，以降 HAM）があげられる。しかし，キャリアだからといって多くの人は発症せず，妊娠出産で問題になることは少ない。

ATL は 40 歳以前の発症は珍しく，キャリアのうち年間 1,000 人に 1 人，生涯で約 5% 発症するとされている[14]。しかし，最近では，新薬の登場や骨髄移植により治療成績も改善されつつあるが，発症すると予後不良であり寿命ロスを引き起こす疾患である。

HAM は，キャリアのうち生涯で約 0.25% 発症するとされている[15]。歩行障害や膀胱直腸障害が緩徐に進行することが多く，治療で進行することを遅らせることはできるが止めることはできず，生活の質（QOL）を損ね健康ロスを引き起こす疾患である。

このように，HTLV-1 は私たちの健康寿命を短くする原因になるため，感染予防対策が重要である。

Ⅱ．HTLV-1 感染経路と対策

HTLV-1 はＢ型肝炎ウイルスやヒト免疫不全ウイルス（HIV）のように血漿中や体液中のウイルス自体で感染するのと異なり，感染リンパ球が生きたまま体の中に入り自分の中のリンパ球と細胞同士の接触によりおこる。感染力は弱く，主な感染経路は，1 母子感染，2 性行為による水平感染，および，3 輸血や臓器移植による感染があげられる。

1. 母子感染

母子感染は，1 年程度母乳を与えた場合の母子感染率は約 15-20% とされている。

ⅰ．母乳以外を介した感染

これまでの研究より，母乳を与えない完全人工栄養法でも約 3% 母子感染が成立する[1~5]。母乳以外を介した感染経路が考えられてきたが，経胎盤感染の存在が示唆されている[16]。この経路を防止する有効な手段は現在ない。

ⅱ．母乳を介した感染

母乳中には感染リンパ球が多く含まれる[17]，母乳を介した感染が証明され[9]，感染予防のため，完全人工栄養法[18]，短期母乳栄養法[19]，凍結解凍母乳法[20]が行われてきた。わが国で初めてのコホート研究で，短期母乳栄養法 2.3%（95% 信頼区間：0.0-4.6%），完全人工栄養法 6.4%（95% 信頼区間：1.9-10.9%）と両者に統計学的な差は認められなかった[4]。母乳以外を介した感染率を考慮すると母乳を介した感染は栄養法を選択することで防止することが可能であると考えられる。

2. 性行為による感染

精液中に多くの感染リンパ球が含まれており[17]，傷ついた粘膜に精液や血液のリンパ球が接触することで感染すると考えられている。男性から女性が優位な経路になる。献血者のデータから HTLV-1 陽転化割合は女性が 10 万人あたり 6.88 人，男性が 10 万人あたり 2.29 人であった[21]。この経路を防止するのは，HTLV-1 に限らず他の性行為感染症と同様に挙児希望無い場合には，エビデンスは乏しいがコンドームの使用が有効と考えられる。

3. 輸血，臓器移植による感染

血液や臓器中の感染リンパ球を介しての感染である。1986 年以降献血での HTLV-1 抗体検査が実施されているため安全に輸血が可能である。2000 年以降，臓器移植後早期に HAM を発症した症例が報告された[22]。キャリアをドナーとした移植には制限がある。

Ⅲ．母子感染対策での支援

1. 産科施設での支援（妊婦健康診査でのスクリーニング検査から栄養法選択と達成まで）

ⅰ．スクリーニング検査からキャリアの確定まで（図 1）

スクリーニング検査陽性の場合に確認検査をしなければキャリアであると判定できないことを伝え，ラインブロット（LIA）法の確認検査を行う。流行地であった鹿児島でも 2018 年には，スクリーニング検査陽性者 69 人のうち確認検査での陽性者は 47 人（68.1%）にとどまっている[23]（**図 2**）。スクリーニング抗体が陽性で確認検査が陰性となる割合は，キャリアが少ない地域では高くなり，非流行地域では 7 割以上陰性とも報告されている[3]。

確認検査が陽性であればキャリアとして，母子感染

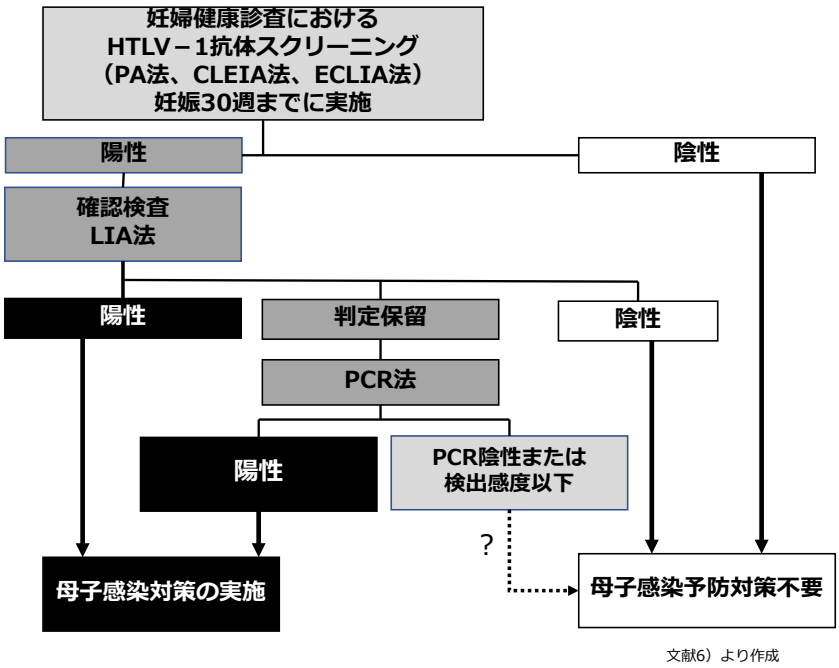

図１　妊婦健診における HTLV-1 抗体検査の流れ

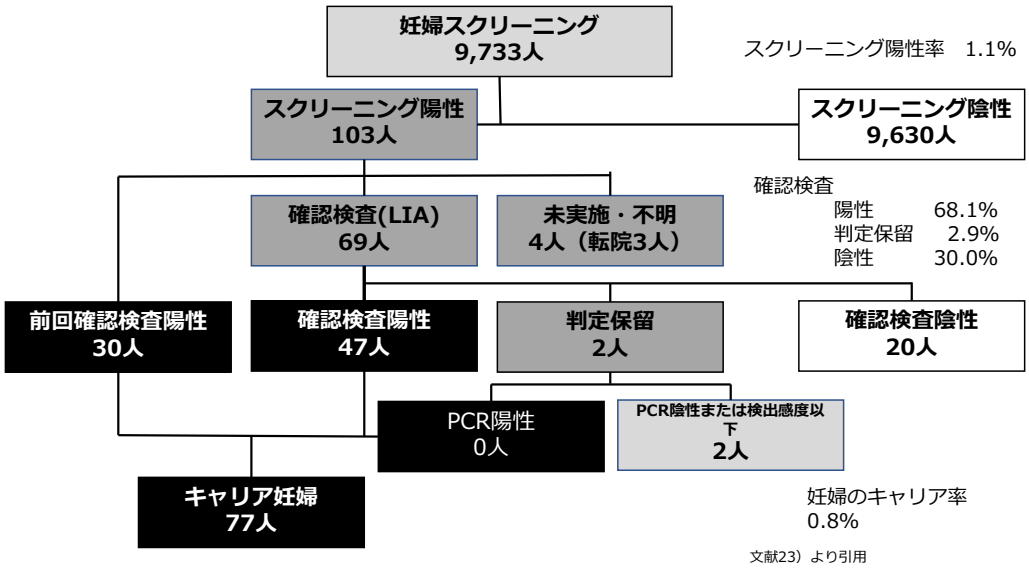

図２　鹿児島県における妊婦への HTLV-1 検査実施状況（令和元年度）

対策を含め情報提供を行う。キャリアは児への感染防止と共に自身が将来発病する可能性で不安となるため[24]，心理的サポートを開始することが必要である。多くのキャリアマザーが相談できずに悩みを抱えている現状がある[25]ため，保健医療者から話しやすい環境を作っていくことが求められる。

一方，確認検査で「判定保留」となる確率は減ったが一定数存在する。2016 年から「判定保留」であった妊婦に限り PCR 法が保険適用された。PCR 法で「陽性」であればキャリアとして扱う。「陰性もしくは検出感度以下」の場合には母子感染の可能性は低いと推定されるがエビデンスが確立していない[6]。授乳で感染症例もあった[26]ため，キャリアではないとはいえず対応が難しい。

ⅱ．キャリアの確定から栄養法選択と達成への支援

キャリアであった場合，感染防止のため栄養法の選択を行う。充分な説明や栄養法選択の意志決定支援を受けた母親では，産後 1 か月，および 3 か月のエジンバラ産後うつ病評価尺度（EPDS）は差を認めず，また EPDS が 9 点以上を示す割合も一般的な妊婦に比

	母乳	人工栄養（ミルク）
児	最適な成分組成で少ない代謝負担 感染症の発症および重症度の低下 小児期の肥満や2型糖尿病の発症リスクの低下 乳児突然死症候群のリスクが下がる 喘息やアトピー性皮膚炎のリスクの低下	ビタミンD,Kや鉄分などが不足しにくい
母親	産後の母体の回復の促進 衛生的、経済的で手間もかからない	父親も授乳に参加できる 授乳量が測定しやすい

図３　母乳と人工栄養（ミルク）の児と母親のメリット

栄養方法	完全人工栄養	短期母乳栄養（90日未満）	凍結解凍母乳栄養	長期母乳栄養
母子感染予防効果	母乳を介した母子感染を予防するためには最も確実な方法（母子感染率約3%）	完全人工栄養と比較して明らかな差がない 達成できる環境では母子感染予防対策として推奨できる	エビデンスとしては少ない （早産児に対して考慮する）	母子感染率約15～20%。 母子感染予防対策としては推奨されない
メリット	最も確実である	母乳のメリットをある程度得ることができる 直接授乳が可能	母乳のメリットをある程度得ることができる 母乳が出る限り与えることができる	母乳のメリットが得られる
デメリット	完全人工栄養購入費がかかる（約10万円） 母乳のメリットが得られない 直接授乳ができない	90日未満しか与えることができない 完全人工栄養に90日未満で移行完了するのに困難がある 助産師等の支援が必要である	パック購入費がかかる（約10万円） 凍結解凍の手間がかかる 直接授乳ができない	感染する確率が上がる

図４　各栄養法の母子感染予防効果とメリット・デメリット

べて高くなかったことから，十分な説明や支援が重要であると考えられる[27]。

母乳を介した感染を防ぐ意味では完全人工栄養法が最も確実である。しかし，母乳育児は母子ともに多くのメリットがある[28]（図３）。そのため短期母乳栄養法が検討され，コホート研究でのエビデンスより今回のマニュアル改訂で短期母乳栄養法も選択肢として含むことになった[6]。また，凍結解凍母乳栄養法も検討されたが，症例数が少なくエビデンスが不十分とし選択肢には含められなかったが早期産児などが選択する可能性がある。母子感染予防よりも母乳栄養のメリットから長期母乳栄養法を選択する母親も存在する。母親および家族が何を重視するかによって選択肢は変わってくる。

そのため保健医療従事者は，自身の価値観にとらわれることなく，感染防止についての情報と共に，各栄養法のメリットと困難さなどのデメリットの情報（図４）を提供し，母親と家族から何を重視するかを聞いて，どの栄養法を選択するかの意思決定支援をおこなう。

どの栄養法を選択しても母親は選択後も自分の選択が正しかったのかと揺れ動いている。出産まではいつでも変更できることを伝える。出産後は栄養法変更が難しいため，正しい選択であったと支持的な対応を行い，選択した栄養方法を達成できるように支援を行う。栄養法を実施するにあたり，選択栄養法によらず約３割が困難を抱えていた[29]。

選択をするにあたり，出生時に児の検査を行い感染していたら母乳を与えたいという希望があることもある。抗体検査は移行抗体により陽性となり，PCR 検査も陰性であっても感染する可能性があるため出生時に検査での判断はできない。

a. 完全人工栄養法

困難を感じた理由の多くは「周囲の理解不足」だった[29]。産婦人科外来には，母乳育児を推奨するポスターも多く，母親学級で授乳指導や出産後授乳する人との同室などがストレスであった。産科スタッフはそのようなストレスがあることを知り配慮することが望まれる。

また，退院後にキャリアであることを知らない人から「母乳がでないの？」といわれストレスだったと言うこともあったため，一般の方への啓発活動が重要であるが難しい。せめて身近な人から言われないように，キャリアであることをどこまで伝えるかも栄養法選択と共に相談して決めていくことが必要である。栄養法選択時点では伝えることができなくても，出産後に関係性をつくり家族の理解と協力を得られるように母親の気持ちに寄り添いながら支援することも重要である。

一方，完全人工栄養法と決定していた場合に早産となった場合，壊死性腸炎の予防などで母乳を与えることを検討することがある。早産児に人工栄養を与えての壊死性腸炎発症など生命的リスクと，凍結母乳栄養

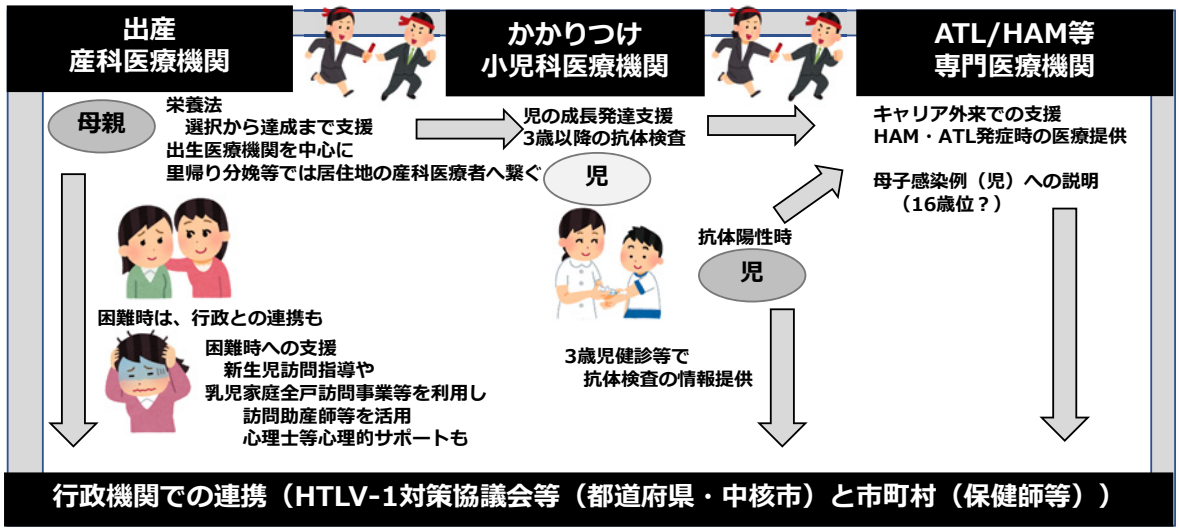

図 5　母子保健分野での医療機関および行政支援体制

法のエビデンスは少ないが理論的には HTLV-1 感染のリスクをよく説明して母親に納得の上，選択してもらう。

b. 短期母乳栄養法

本栄養法の困難は，やはり 90 日未満で人工栄養への完全な移行の達成である。ひとりで達成するのは困難で，支援が無ければ 5 人に 1 人やめられない可能性がある[4]。その理由は乳房トラブルなど技術的支援不足であった[29]。産後 1 か月健診で支援が途切れていることが多かったが，鹿児島県では短期母乳栄養法を選択した場合に，約半数が「3 か月後の断乳を確認した」と回答していた[23]。出産した産科施設で母親も慣れているため 1 か月以降も継続して，人工栄養への完全移行達成の確認まで支援を続けるのが望ましい。もしも，里帰り分娩等の場合で難しい場合には，本人の同意のもと居住地近くの産科医療機関や開業助産師へ紹介するか，居住地の保健師につなぎ，新生児訪問指導や乳児家庭全戸訪問事業（こんにちは赤ちゃん事業）で助産師の活用を依頼することを検討し，途切れることがない支援体制を作る。

また，「そんなに泣くならあげたら」と夫に言われ心が折れたと話す方もいたので，移行時に家族の支援も重要であり，理解と協力が得られるように事前に話し合いを持ち準備しておくことが重要である。移行後は，完全人工栄養と同じように他者からの授乳に関するストレスは生じうる。

完全人工栄養法も含め短期母乳栄養法も移行後，約 1 年間で人工栄養購入費が 10 万円ほどかかる。経済的理由から長期母乳を選択する家族もいた。鹿児島県では 2019 年以降の一部助成が行われている[30]。健康社会格差解消のために HTLV-1 キャリアだけでなく，本人の意思によらない理由で母乳を与えることができない方への支援を検討する必要がある。

c. その他の栄養法

母親と家族に説明後，十分考え抜いた末に「長期母乳栄養法」や「凍結母乳栄養法」を選択することもある。自身がアレルギー体質で悩んでこられ，母乳をあげないことで HTLV-1 関連疾病の発症するリスクと母乳をあげることでのアレルギー発症のリスク軽減から，長期母乳栄養法を選択された母親がいた。絶対に正しい栄養法はなく，本人の価値観により正しい選択肢は変わってくる。本人が納得できる選択をした際に達成できるよう支援することが重要である。

ⅲ．切れ目ない支援へ（図 5）

2010 年に妊婦スクリーニング検査が開始後，産科施設での支援は充実してきている。しかし，産後 1 か月健診以降は途切れること[23]の課題がある。そのため，次項にある小児医療施設での支援と行政機関での支援に診療情報提供書等でつないでいく。母体・児の一般的な情報以外に，抗体検査の情報，選択栄養法，キャリアであることを知っている家族の範囲が有効な情報になる。

2. 小児医療施設での支援（産科医療施設からの紹介から内科医療施設紹介まで）（図 5）

キャリア妊婦より出生した児を産科医療機関等から

の紹介を受ける。小児期において南米でHTLV-1関連の神経症状[31]や皮膚症状[32]の報告があるが，我が国ではほぼ報告がない。人種差なのかその差を説明する要因は不明である。他の小児と同じように定期予防接種や健診をすすめていくが，母子感染の有無の確認についての説明が必要になる。

母子感染の確認は，3歳以降に妊婦健診と同様の方法でスクリーニング検査を実施する。移行抗体消失後3歳までに抗体が陽転することから[33]，それ以前に検査して陰性であってもその後陽性になる可能性があるため，勧められない。

3歳以降に検査を実施すれば，約97%の確率で母子感染していなかったと判断できる。母親も自分が行った感染対策の成果があったことを確認でき満足度も高く，母親の不安を取るという大きなメリットがある。しかし，母乳以外の経路での感染が約3%あり，母子感染したことを知った母親のショックは大きい。十分なカウンセリングと児が理解できる年齢に達したときに，告知と情報提供の機会を確保する必要がある。HTLV-1は妊娠・母乳をあげる・性行為・臓器移植など特別な関係での行為以外の日常生活で他の人に感染させることはないため，性活動期が始まるまでは特別な感染防止策は必要ない。そのため児の所属する施設・学校等へのキャリアであることの情報提供は必要ない。

児がキャリアであることを知るメリットは，性活動期前に男女ともパートナーを守るためにHTLV-1に限らず性感染予防のためにコンドームの使用の重要性の教育，女性は妊娠後限られた時間ではなく事前に情報を得て判断する時間の確保ができることが考えられる。偶発的に児が感染を知る機会として献血がある。献血時希望すればHTLV-1感染には親展郵便で通知される[34]。著者の経験であるが妊婦健診で分かる前に，1割ほどが献血で既に知っていた。しかし，多くは同封の資料では理解できず，かつ親を含め誰にも相談せず一人で悩み，中にはHIVと勘違いして自殺を考えたものがいたため，事前に告知し説明する機会を確保することができるのはメリットになるかもしれない。しかし，HTLV-1に関しての国民の理解が十分でないためキャリアへの負担が多く，3歳時に検査をして陽性であればその後に告知を行うことは，約3%と少数ではあるが「知らされない」という児の自己選択権を侵害する可能性もあり，判断が難しい。

3歳児に理解して自己決定してもらうことが難しいため，一つの方法として本人がHTLV-1感染のことを理解できるようになった時，目安として性活動期が活発化や献血をすることができる16歳よりも前に，「母親がキャリアであり，子どものことを考えて栄養法を選択した」，「その栄養法を選択しても，一定の割合で母子感染してしまう」，「検査でキャリアであるかは知ることができる」，「キャリアである場合には性行為の際にコンドームの使用でパートナーに感染するのを減らすことができる」，「将来子どもに関しては栄養法を選択することで母子感染リスクを下げることができる」等の事柄を伝え，児に選択してもらう方法もあると考える。母子感染の有無の確認の検査は，母親および家族の価値観で検査の時期，実施するかしないかを決めることになる。

母子感染予防のため栄養法を達成した後，安堵と共に自身がキャリアであることの不安が再度湧き上がってくることがある。日本HTLV-1学会では登録医療機関制度を設けて，HTLV-1に関連した相談対応が可能な施設を認定して公開している[35]。2021年5月時点で16機関中九州・沖縄に10機関と偏在しているが，現在も登録募集を行っているので今後増えていくことが期待される。また，登録されている医療機関がない場合には，厚生労働省は各都道府県や政令指定都市に対して，HTLV-1母子感染対策協議会を設置し体制整備を推進している[36]ので，問い合わせてみるとよい。

3. 行政機関（各都道府県や政令指定都市，市町村）での支援（医療機関との連携）（図5）

各都道府県や政令指定都市はHTLV-1母子感染対策協議会を設置し，妊婦に対するHTLV-1抗体検査の適切な実施，相談窓口，母子感染に関する普及啓発，医療機関連携，体制整備，評価などを行うことになっている。産科医療機関でキャリアと判明した場合には，本人の同意を得て，富山県[37]をはじめ未熟児等出生連絡票を用いたり，鹿児島県[38]のように専用の情報提供書を用いたりして連携をとっている地域もある。

各都道府県や政令指定都市は，自治体内の出生数と妊婦の感染率から，年間のキャリア妊婦の数，母子感染者数，将来の発症者数を推定し母子感染対策の体制整備が必要である。例えば，鹿児島県では令和元年度11,977出生数で感染率が0.8%から，年間のキャリア妊婦の数は約100人，3年後の母子感染者は3人，

HTLV-1 関連疾患の発症者は 5 人と推定される。流行地であった鹿児島県でも数が減っているため，非流行地域では更に少ないと考えられる。そのため各都道府県や政令指定都市を中心とした整備が重要である。

産科医療機関より情報提供があった際には，市町村の保健師による支援を行う。新生児訪問指導や乳児家庭全戸訪問事業（こんにちは赤ちゃん事業）など既存の事業を利用し，短期母乳栄養法で乳房のことで不安を抱えている場合には助産師など産科医療関係者，心理的な不安に関しては臨床心理士など精神医療関係者など専門職を活用し，必要なサービスにつなげる。

3 歳児健診時には，3 歳以降検査が可能であり，そのメリット・デメリットを含め情報提供を行い，母親および家族の選択を支援する。決して検査実施を強制してはならない。また，キャリアであることの不安や母子感染した症例やキャリアである母親を各都道府県や政令指定都市が整備したカウンセリングや診療体制へ適切につなぐことも必要である。

おわりに

HTLV-1 総合対策として全国で妊婦の抗 HTLV-1 抗体検査が全例公費負担で実施されるようになり 10 年が経過した。産科医療施設での支援体制は整備されつつあるが，今回のマニュアル改訂で短期母乳栄養法選択者への支援を新たに整備する必要がある。今後，小児保健関係者は所属機関は異なっても互いの支援内容を理解し，産科医療施設から小児医療施設，内科等専門医療施設への医療機関同士の連携，また都道府県と市町村の行政機関内同士での連携を行うことが求められる。医療機関と行政機関を中心に社会での総合的な HTLV-1 キャリア支援を多方面から行うことで，キャリアマザーと児が脱落しない体制が構築されることを期待したい。

文　献

1）厚生労働科学研究費補助金・厚生労働科学特別研究事業「HTLV-1 の母子感染予防に関する研究」（研究代表者：齋藤滋）．HTLV-1 母子感染予防対策医師向け手引き．2011

2）厚生労働科学研究費補助金・厚生労働科学特別研究事業「ヒト T 細胞白血病ウイルス-1 型（HTLV-1）母子感染予防のための保健指導の標準化に関する研究」（研究代表者：森内浩幸）．HTLV-1 母子感染予防対策保健指導マニュアル．2011

3）厚生労働行政推進調査事業費補助金・成育疾患克服等次世代育成基盤研究事業「HTLV-1 母子感染予防に関する研究：HTLV-1 抗体陽性妊婦からの出生児のコホート研究」（研究代表者：板橋家頭夫）．HTLV-1 母子感染予防対策マニュアル．2017

4）Itabashi K, Miyazawa T, Nerome Y, et al. Issues of infant feeding for postnatal prevention of human T-cell leukemia/lymphoma virus type-1 mother-to-child transmission. Pediatr Int 2021; 63: 284-289.

5）Miyazawa T, Hasebe Y, Murase M, et al. The Effect of early postnatal nutrition on human T cell leukemia virus type 1 mother-to-child transmission: a systematic review and meta-analysis. Viruses 2021; 13: 819.

6）厚生労働科学研究費健やか次世代育成総合研究事業補助金．「HTLV 1 母子感染対策および支援体制の課題の検討と対策に関する研究」（研究代表者：内丸薫）．HTLV-1 母子感染予防対策マニュアル．2022

7）Uchiyama T, Yodoi J, Sagawa K, et al. Adult T-cell leukemia: clinical and hematologic features of 16 cases. Blood 1977; 50: 481-492.

8）Hinuma Y, Nagata K, Hanaoka M, et al. Adult T-cell leukemia: antigen in an ATL cell line and detection of antibodies to the antigen in human sera. Proc Natl Acad Sci USA 1981; 78: 6476-6480.

9）Hino S, Yamaguchi K, Katamine S, et al. Mother-to-child transmission of human T-cell leukemia virus type-I. Jpn J Cancer Res 1985; 76: 474-480.

10）中嶋有美子，森内浩幸．各地域の母子感染予防対策の実際：長崎県．周産期医学　2020; 50(10): 1758-1760.

11）根路銘安仁．各地域の母子感染予防対策の実際：鹿児島県．周産期医学　2020; 50(10): 1755-1757.

12）厚生省心身障害研究「成人 T 細胞白血病（ATL）の母子感染防止に関する研究班」（主任研究者：重松逸造）平成 2 年度研究報告書．1991

13）厚生労働科学研究費補助金新興・再興感染症研究事業「本邦における HTLV-1 感染及び関連疾患の実態調査と総合対策」（研究代表者：山口一成）．2009

14）Iwanaga M. Epidemiology of HTLV-1 Infection and ATL in Japan: An Update. Front Microbiol 2020; 11: 1124.

15）Bangham CR, Araujo A, Yamano Y, et al. HTLV-1-associated myelopathy/tropical spastic paraparesis.

Nat Rev Dis Primers 2015; 1: 15012.
16）Tezuka K, Fuchi N, Okuma K, et al. HTLV-1 targets human placental trophoblasts in seropositive pregnant women. J Clin Invest 2020; 130(11): 6171-6186.
17）Nakano S, Ando Y, Ichijo M, et al. Search for possible routes of vertical and horizontal transmission of adult T-cell leukemia virus. Gan 1984; 75: 1044-1045.
18）Hino S, Sugiyama H, Doi H, et al. Breaking the cycle of HTLV-1 transmission via carrier mothers' milk. Lancet 1987; 2: 158-159.
19）Hirata M, Hayashi J, Noguchi A, et al. The effects of breastfeeding and presence of antibody to p40tax protein of human T cell lymphotropic virus type-I on mother to child transmission. Int. J. Epidemiol. 1992; 21: 989-994.
20）Ando Y, Kakimoto K, Tanigawa T, et al. Effect of freeze-thawing breast milk on vertical HTLV-I transmission from seropositive mothers to children. Jpn. J. Cancer Res. 1989; 80: 405-407.
21）Satake M, Iwanaga M, Sagara Y, et al. Incidence of human T-lymphotropic virus 1 infection in adolescent and adult blood donors in Japan: a nationwide retrospective cohort analysis. Lancet Infect Dis 2016; 16: 1246-1254.
22）Yamauchi J, Yamano Y, Yuzawa K. Risk of human T-cell leukemia virus type 1 infection in kidney transplantation. N Engl J Med 2019; 380: 296-298.
23）根路銘安仁．鹿児島県における HTLV-1 母子感染対策の検討．厚生労働科学研究費補助金（成育疾患克服等次世代育成基盤研究事業（健やか次世代育成総合研究事業））（研究代表者：内丸薫）．令和 3 年度分担報告書．2022
24）谷口光代，根路銘安仁，北村　愛，他．HTLV-1 キャリア妊産婦からの相談内容-鹿児島県の保健師および助産師への調査結果から．インターナショナル Nursing Care Research　2016; 15: 73-82.
25）柘植　薫．キャリアマザーに対する臨床心理学的アプローチ-HTLV-1 がキャリアマザーに及ぼす心理的影響について．周産期医学　2020; 50: 1730-1733.
26）Nerome Y, Yamamoto N, Mizuno M, et al. A case of mother-to-child transmission of human T-cell leukemia virus type-1 from a polymerase chain reaction negative mother. Pediatr Int. 2021; 63(11): 1383-1384.
27）宮沢篤生．HTLV-1 キャリア女性における乳汁栄養の選択がメンタルヘルスに及ぼす影響．厚生労働科学研究費補助金（成育疾患克服等次世代育成基盤研究事業）「HTLV-1 母子感染予防に関する研究：HTLV-1 抗体陽性母体からの出生児のコホート研究」（研究代表者：板橋家頭夫）平成 27 年度分担研究報告書．2015
28）Arthur IE, Richard JS, Margreete J, et al. Section on breastfeeding. breastfeeding and the use of human milk. Pediatrics 2012; 129(3): 827-841.
29）Nerome Y, Owaki T, Amitani M, et al. HTLV-1 carrier mothers need continual support to accomplish their selected nutrition method for mother-to-child transmission prevention in Kagoshima. Med J Kagoshima Univ 2015; 67: 51-57.
30）鹿児島県．"鹿児島県 HTLV-1 等母乳を介する母子感染対策推進事業について"．https://www.pref.kagoshima.jp/ae06/kenko-fukushi/kenko-iryo/kansen/atl/htlv-1miruku.html（参照 2022.03.15）
31）Kendall EA, Gonzalez E, Espinoza I, et al. Early neurologic abnormalities associated with human T-cell lymphotropic virus type 1 infection in a cohort of Peruvian children. J Pediatr 2009; 155(5): 700-706.
32）Maloney EM, Wiktor SZ, Palmer P, et al. A cohort study of health effects of human T-cell lymphotropic virus type i infection in jamaican children. Pediatrics 2003; 112(2): 136-142.
33）Kusuhara K, Sonoda S, Takahashi K, et al. Mother-to-child transmission of human T-cell leukemia virus type I (HTLV-I): a fifteen-year follow-up study in Okinawa, Japan. Int J Cancer 1987; 40(6): 755-757.
34）日本赤十字社．"HTLV-1 抗体検査の結果についてのお知らせ"．https://www.bs.jrc.or.jp/bc9/bbc/special/m6_05_04_index.html（参照 2022.03.15）
35）日本 HTLV-1 学会．"日本 HTLV-1 学会登録医療機関（2021 年 5 月時点）"．http://htlv.umin.jp/info/hospital.html（参照 2022.03.15）
36）厚生労働省．"第 8 回 HTLV－1 対策推進協議会 資料 2　HTLV-1 母子感染対策事業の取組状況について"．https://www.mhlw.go.jp/file/05-Shingikai-10901000-Kenkoukyoku-Soumuka / 0000077307. pdf （参　照 2022.03.15）

37）富山県．“富山県 HTLV-1 母子感染対策対応マニュアル（第 4 版）”．https://www.pref.toyama.jp/documents/17658/01222285.pdf（参照 2022.03.15）
38）鹿児島県．“HTLV-1 感染対応マニュアル（令和 3 年 3 月）”．http://www.pref.kagoshima.jp/ae06/kenko-fukushi/kenko-iryo/kansen/atl/documents/2935_20210326184443-1.pdf（参照 2022.03.15）

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EDITED BY
Wei Zhang,
University of Minnesota Twin Cities,
United States

REVIEWED BY
Yorifumi Satou,
Kumamoto University,
Japan
Philippe V. Afonso,
Institut Pasteur,
France

*CORRESPONDENCE
Kiyonori Miura
kiyonori@nagasaki-u.ac.jp

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Frequency of HTLV-1 seroconversion between pregnancies in Nagasaki, Japan, 2011–2018

Nahoko Komatsu[1], Masako Iwanaga[2], Yuri Hasegawa[1], Shoko Miura[1], Naoki Fuchi[1], Hiroyuki Moriuchi[3], Katsunori Yanagihara[4] and Kiyonori Miura[1]*

[1]Department of Obstetrics and Gynecology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [2]Department of Clinical Epidemiology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [3]Department of Pediatrics, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [4]Department of Laboratory Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Background: Human T-cell leukemia virus type-1 (HTLV-1) is transmitted vertically from an infected mother to her child *via* breastfeeding during infancy or horizontally *via* sexual contact. However, little information is available on the HTLV-1 seroconversion rate in pregnant mothers and the impact of new HTLV-1 infection on mothers and babies during the perinatal period.

Methods: From the database of a prefecture-wide antenatal adult T-cell leukemia prevention program in Nagasaki, Japan, we extracted data on 57,323 pregnant women who were screened for anti-HTLV-1 antibody during 2011–2018. Data on the 16,863 subjects whose HTLV-1 proviral load (PVL) was measured more than twice were included in our analyses.

Results: In total, 133 (0.79%) pregnant women were HTLV-1-positive during their first pregnancy and nine (0.05%) seroconverted before or during subsequent pregnancies (between pregnancies). The median PVL (per 100 peripheral blood mononuclear cells) was significantly lower in the seroconverted mothers (0.10%) than in the initially seropositive mothers (0.15%). A repeated measures correlation analysis for the individual PVLs of the HTLV-1-positive pregnant women showed that PVL increased with parity number (rrm=0.25) with no perinatal problems.

Conclusion: The HTLV-1 seroconversion rate between pregnancies was 0.05%, and their HTLV-1 PVL increased annually but no perinatal problems were noted.

KEYWORDS

HTLV-1, pregnant woman, carrier, screening test, seroconversion, horizontal transmission, proviral load, adult T-cell leukemia-lymphoma

Introduction

Human T-cell leukemia virus-1 (HTLV-1) is a retrovirus that causes adult T-cell leukemia (ATL), HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), and a variety of HTLV-1-associated inflammatory disorders (Watanabe, 1997). Globally, HTLV-1 infects at least 5–10 million people (Gessain and Cassar, 2012), particularly in southwest Japan, Brazil, the Caribbean islands, Central and South America, sub-Saharan Africa, and central Australia (Gessain and Cassar, 2012; World Health Organization, 2020). HTLV-1 infects mainly CD4-positive T-cells and is known to transmit from person-to-person *via* cell-to-cell contact between HTLV-1-infected cells and uninfected cells through three modes (Bangham, 2003; Matsuoka and Jeang, 2007; Pique and Jones, 2012): vertical mother-to-child transmission from HTLV-1-infected mothers *via* breastfeeding (Hino et al., 1985), horizontal transmission from HTLV-1-infected partners *via* sexual intercourse (Stuver et al., 1993; Kaplan et al., 1996; Roucoux et al., 2005; Satake et al., 2016; Paiva et al., 2017), and iatrogenic transmission *via* HTLV-1-infected donated blood or organs. However, the risk of iatrogenic transmission through transfusion can be reduced by performing leukoreduction prior to transfusion (Okochi et al., 1984; Armstrong et al., 2012).

The first scientific evidence of vertical transmission from a HTLV-1-infected mother to their infant *via* prolonged breastfeeding by the infected mother was presented in 1985 by researchers from Nagasaki University, located in southwest Japan (Hino et al., 1985; Figure 1). They presented the following findings: (1) the first nationwide survey of HTLV-1 infection in Japan identified Nagasaki Prefecture as one of the regions with the highest prevalence of HTLV-1-infected individuals (Tajima et al., 1982); (2) HTLV-1-infected cells are present in breastmilk from HTLV-1-carrier mothers, and infection through breastfeeding is associated with a higher probability of developing ATL (Kinoshita et al., 1984); and (3) experimentally, HTLV-1 can be transmitted *via* intraoral inoculation among common marmosets (Kinoshita et al., 1985; Yamanouchi et al., 1985). Soon after, a prefecture-wide, multidisciplinary, antenatal intervention program, known as the "ATL Prevention Program (APP)," was established in 1987 in Nagasaki (APP Nagasaki; Hino et al., 1987) through collaboration with virologists, obstetric gynecologists, hematologists, pediatricians, and clinical laboratory scientists at Nagasaki University, obstetric gynecologists throughout Nagasaki Prefecture, and public health officers of the Maternal and Child Health Division (MCHD) of the Nagasaki Prefectural Government. The purpose of APP Nagasaki was to reduce the vertical transmission of HTLV-1 *via* breastfeeding and to reduce the future development of HTLV-1-associated diseases through systematic screening for anti-HTLV-1 antibodies in pregnant women and the avoidance

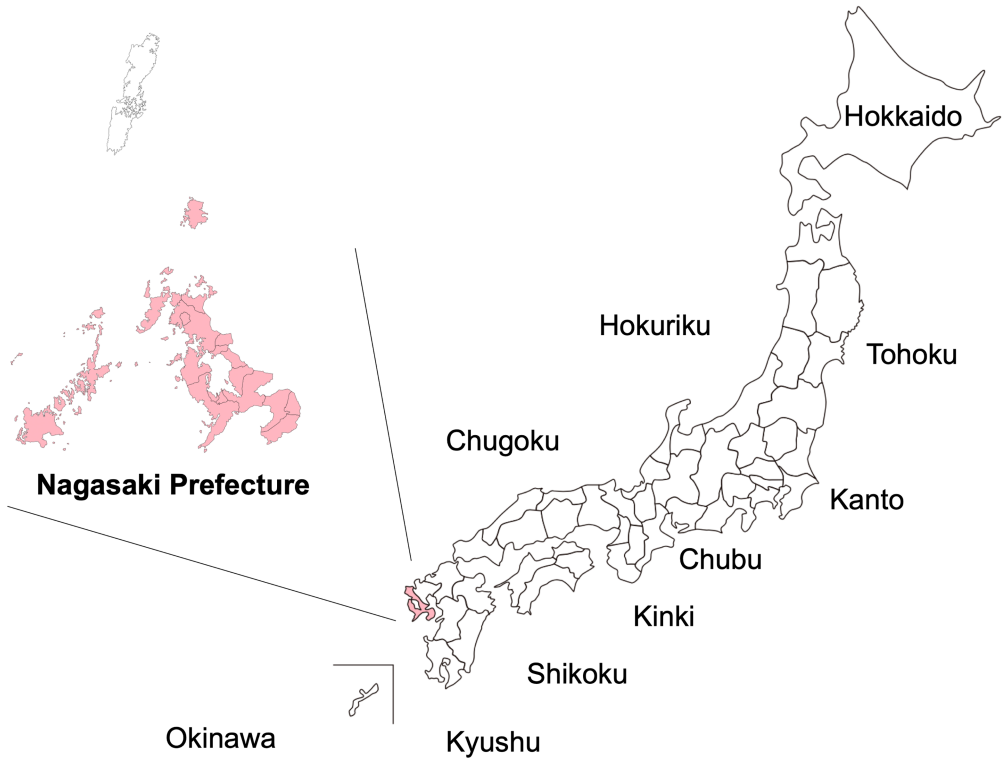

FIGURE 1
Location of the study area in Nagasaki Prefecture, Japan. The present study was carried out in Nagasaki Prefecture, which is located in the most western part of Japan. Only the part of Nagasaki Prefecture colored pink is included in this study. (Tsushima islands are not included).

of breastfeeding in identified HTLV-1-infected mothers, in Nagasaki Prefecture.

As previously reported, APP Nagasaki led to a marked reduction in mother-to-child HTLV-1 transmission rates from 20.5% before the APP began to 2.4% after its implementation (Hino et al., 1997; Katamine, 1999; Hino, 2011; Moriuchi et al., 2013; Miura and Masuzaki, 2017). Other intervention programs similar to APP Nagasaki have been implemented in several areas endemic for HTLV-1 in Japan (Takahashi et al., 1991; Kashiwagi et al., 2004). However, HTLV-1 infection is currently widespread across geographical regions (Watanabe, 2011; Satake et al., 2012), and the number of HTLV-1 carriers in the metropolitan areas in Japan has increased. This situation probably reflects the migration of individuals from HTLV-1-endemic areas (Watanabe, 2011). A nationwide antenatal screening program for HTLV-1 was introduced in Japan in 2011 (Itabashi et al., 2020). Currently, it is estimated that each year ~1,600 HTLV-1-infected pregnant mothers in Japan (almost 0.16% of all pregnant mothers in Japan; Suzuki et al., 2014) are recommended to refrain from breastfeeding to avoid mother-to-child HTLV-1 transmission by methods similar to that of APP Nagasaki.

Recently, researchers from APP Nagasaki reported that the HTLV-1 proviral load (PVL), induced regulatory T-cell population, and soluble interleukin-2 receptor (sIL-2R) levels of HTLV-1-infected pregnant mothers remained stable during pregnancy but became elevated after delivery (Fuchi et al., 2018). However, many questions regarding the impact of HTLV-1 infection on pregnant mothers remain unanswered. For example, the number of pregnant mothers who seroconvert from HTLV-1 negative to positive between pregnancies, how the HTLV-1 PVL changes in HTLV-1-infected pregnant mothers through delivery (between pregnancies), and the specific risks to pregnancy outcomes for HTLV-1-infected and HTLV-1-seroconverted mothers are not currently known.

The present study therefore aimed to assess the HTLV-1 seroconversion status in multiparous mothers who participated in APP Nagasaki, the individual changes of the HTLV-1 PVL between pregnancies in HTLV-1-positive mothers, and the impact of HTLV-1 positivity on pregnancy outcomes.

Materials and methods

Study area and database

From its initiation in July 1987 to April 2018, the APP Nagasaki database included information on ~330,000 pregnant mothers, from almost all areas of Nagasaki Prefecture, who were tested for HTLV-1 infection (Figure 1). The database is managed by the Department of Obstetrics–Gynecology at Nagasaki University Hospital (Miura and Masuzaki, 2017).

Protocol employed for APP Nagasaki

Figure 2 shows the protocol employed for APP Nagasaki (Miura and Masuzaki, 2017). Briefly, any pregnant mothers who were ~30 weeks of gestation and living in most areas of Nagasaki Prefecture were asked to participate in APP Nagasaki when visiting their obstetric gynecologists. After providing consent to participate in the project, each pregnant mother was required to provide a blood sample for an anti-HTLV-1 antibody test. From 2011 onwards, such blood samples were sent to one of five commercial clinical laboratory companies (see Acknowledgment) where a screening test for anti-HTLV-1 antibody was performed using either a particle agglutination (PA) assay, a chemiluminescent immunoassay (CLIA), or a chemiluminescent enzyme immunoassay (CLEIA). The definition of "HTLV-1-positive" as a result of the screening test is a titer of 8 or higher in the PA assay or a cutoff index (COI) of ≥1.0 in the CLEIA or CLIA, in accordance with the manufacturer's criteria (Fujirebio, Japan).

All of the negative screening test results from the clinical laboratory companies were sent back to the respective obstetric gynecologists, for them to inform the respective pregnant mothers. From 2011 onward, in the case of a positive or suspected positive screening test result, the residual blood sample was forwarded to the APP Nagasaki office at Nagasaki University Hospital where a confirmatory test was performed by western blotting and the HTLV-1 PVL was quantified by a real-time polymerase chain reaction (RT-PCR) assay in the Department of Laboratory Medicine. The final test results were reported to the respective obstetric gynecologists, who then informed the respective mothers by 35 weeks of gestation (Figure 2). The obstetric gynecologists also asked their public health nurses to explain to HTLV-1-positive pregnant mothers how to prevent HTLV-1 mother-to-child transmission, preferentially through exclusive bottle-feeding or alternatively by freeze–thawing breast milk or only short-term breastfeeding for no more than 3 months. According to the APP Nagasaki report, the majority of HTLV-1-positive pregnant mothers chose the first choice option of exclusive bottle-feeding to prevent mother-to-child transmission (Miura and Masuzaki, 2017).

Quantification of the HTLV-1 PVL

In APP Nagasaki, a quantitative RT-PCR assay was routinely performed from 2011 onward to quantify the HTLV-1 PVL in peripheral blood mononuclear cells (PBMCs) from anti-HTLV-1 antibody-positive pregnant mothers and those with indeterminate western blotting results. The details of the method used to quantify the HTLV-1 PVL have been previously published (Kamihira et al., 2003; Sasaki et al., 2010), and the resulting value was expressed as the copy number per 100 PBMCs. All measurements were performed by the Department of Laboratory Medicine at Nagasaki University Hospital. Coefficient variation (CV) of HTLV-1

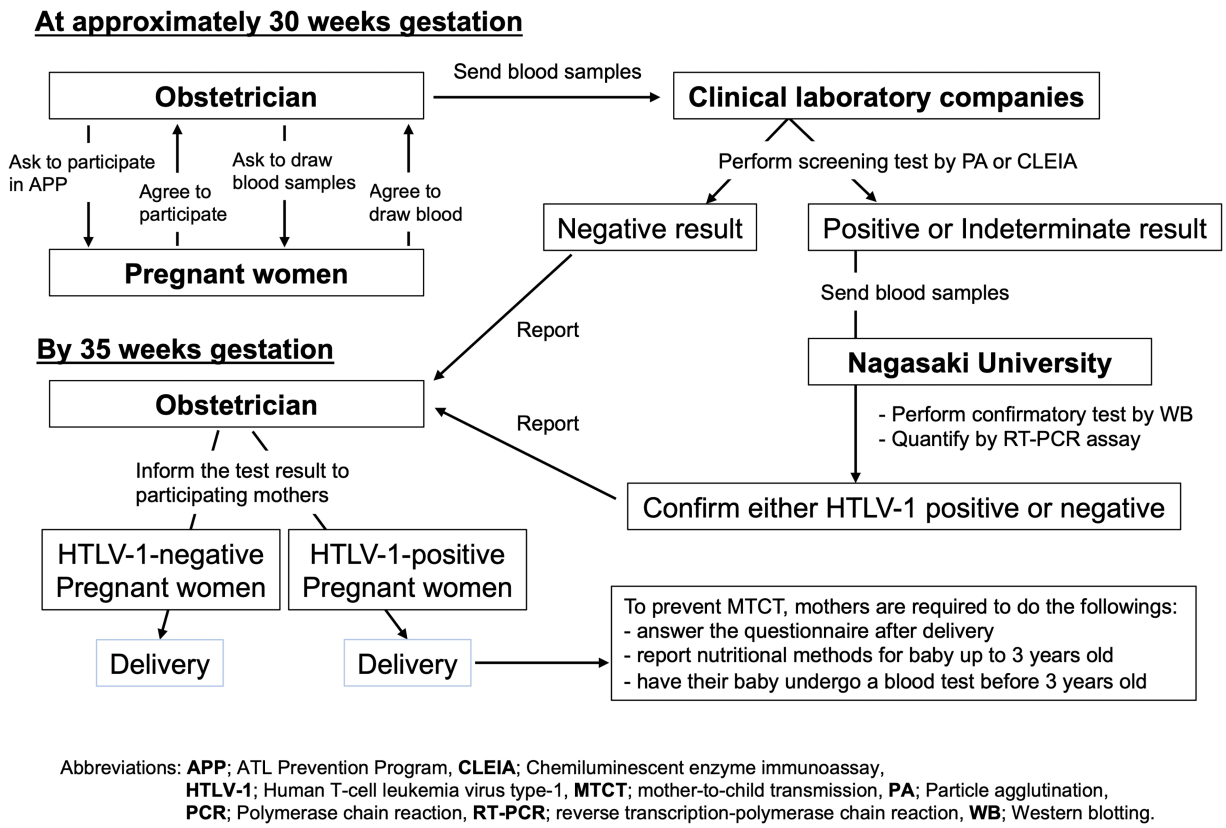

FIGURE 2
Study protocol of the APP Nagasaki project. By 30weeks of gestation, blood samples were obtained from the pregnant mothers who participated in APP Nagasaki to screen for anti-HTLV-1 antibody. Negative test results were reported directly to the respective obstetrician. For positive or indeterminate test results, confirmatory tests were performed. All of the test results were scheduled to be returned to the respective obstetricians by 35weeks of gestation.

quantitative PCR test in Nagasaki university hospital was 13.3% (Kuramitsu et al., 2015).

Questionnaires for HTLV-1-positive mothers and their doctors after delivery

Within 1 week of delivery, each of the HTLV-1-positive mothers who participated in APP Nagasaki was required to answer questions about their birthplace, pregnancy history, the feeding method chosen by their own mother (i.e., the grandmother) during their infancy, and the feeding method that they chose for their own baby. Their obstetric gynecologist was also required to answer questions regarding pregnancy/delivery complications, the health condition of the baby, and the medical history of the pregnant mother (Supplementary material S1).

Data extraction for analysis

The dataset used for analysis in this study was extracted from the APP Nagasaki database after obtaining approval from the Ethics Committee of the Institutional Review Board of Nagasaki University Hospital, Nagasaki, Japan (approval number: 20051810, September 2019). The APP Nagasaki was initiated in 1987, and modern techniques to measure the HTLV-1 PVL using an RT-PCR assay have been applied to participating mothers only since 2011 (Kamihira et al., 2003; Sasaki et al., 2010). Therefore, for the present analysis, we limited our data extraction to the years 2011–2018.

Statistical analysis

We analyzed the available data on pregnant mothers who were tested for HTLV-1 infection at least twice during pregnancy. The demographic data were summarized with standard descriptive statistics, such as frequencies (percentages) for categorical variables, and median (min–max) or median (interquartile range, IQR) values for continuous variables. The pregnant mother age at enrollment in the APP was treated as a continuous variable or categorized into four groups (<25, 26–30, 31–35, and >36 years old). The

method of feeding that the pregnant mothers themselves received from their own mothers was categorized into three groups: long-term breastfeeding (6 months or longer), short-term breastfeeding (shorter than 6 months), and formula feeding alone. The mothers were also categorized into subgroups based on their history of gravidity (the number of pregnancies), parity (the number of live births), and divorce. Continuous variables were compared using Wilcoxon rank-sum tests. Categorical variables were compared using the Chi-squared test or Fisher's exact test, as appropriate. All of the basic statistical analyses were performed using OpenEpi Statistical Software version 3.01 (http://www.openepi.com, Atlanta, GA, United States; Sullivan and Dean, 2009) and R package version 3.4.2 (R-Project for Statistical Computing, https://CRAN.R-project.org). To analyze changes over time in the HTLV-1 PVL by age and by parity of the HTLV-1-positive mothers, we conducted repeated measures correlation (rmcorr) analyses using the R package version 0.3.0 (R-Project for Statistical Computing, https://CRAN.R-project.org; Bakdash and Marusich, 2017) and calculated the correlation coefficient for repeated measures (*rrm*). All statistical tests were performed at the two-tailed 5% level of significance.

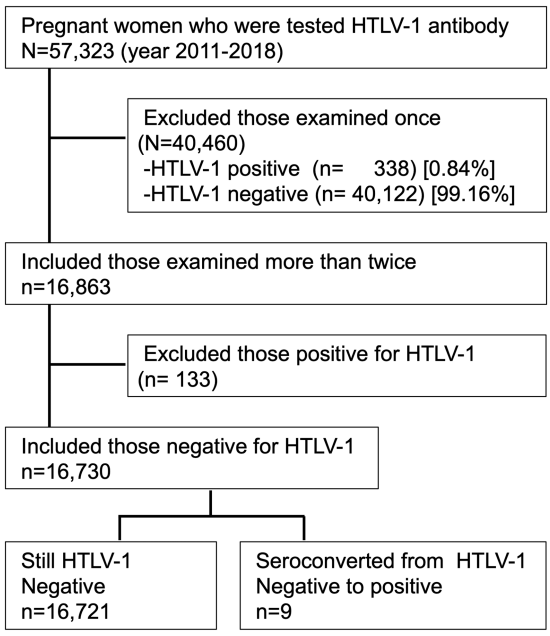

FIGURE 3
Study flowchart for the present analysis. Of the 57,323 pregnant mothers who were screened for anti-HTLV-1 antibody during 2011–2018, the 16,863 mothers who were examined more than twice were included in the study. Of those included, the 16,730 mothers who tested negative for anti-HTLV-1 antibody were included in the analysis. Nine of these women later seroconverted to HTLV-1-positive.

Results

HTLV-1 seropositive status

Figure 3 shows the flowchart for the present analysis. In the years 2011–2018, a total of 57,323 pregnant mothers were screened for anti-HTLV-1 antibody, and 471 (seropositive rate of ~0.82%) were identified as being HTLV-1-positive. Among the 57,323 screened women, 40,460 (70.6%) were examined only once, and the remaining 16,863 (29.4%) were examined more than twice. Of those examined only once, 338 (0.84%) were HTLV-1-positive; of those examined more than twice, 133 (0.79%) were HTLV-1-positive. Among the 133 HTLV-1-positive pregnant mothers screened during their first pregnancy, 61 (45.9%) had already been diagnosed as asymptomatic HTLV-1 carriers in a hospital before their enrollment with APP Nagasaki, but the remaining 72 had no prior HTLV-1 diagnosis information. To date, there have been no reports about ATL, HAM/TSP, or other HTLV-1-associated diseases from their obstetric gynecologists.

HTLV-1 seroconversion rate

During the period between January 2011 and December 2018, nine (0.054%) of the 16,730 pregnant mothers who were found to be negative for HTLV-1 during the initial screening subsequently seroconverted to HTLV-1 positive (Figure 3). Thus, the incidence rate of HTLV-1 seroconversion among HTLV-1-negative pregnant mothers was 17.5 (95% confidence interval: 11.4–26.0) per 100,000 person-years at follow-up.

Background characteristics

Table 1 summarizes the characteristics of pregnant mothers who were already known to be HTLV-1 seropositive before their entry into the study ($n = 133$) and those of mothers who were HTLV-1 seronegative at study entry but later seroconverted to anti-HTLV-1 antibody-positive ($n = 9$). The median age at first entry to APP Nagasaki was 30 years old (range, 17–47 years old) in mothers of known HTLV-1-seropositive status and 31 years old (range, 23–38 years old) in HTLV-1-seroconverted mothers. Although there was no statistically significant difference in the age distribution between the two groups, approximately half of those already known to be HTLV-1-seropositive were in their late 20 s at their first pregnancy, whereas approximately half of the HTLV-1-seroconverted mothers were in their 30 s at their first pregnancy. There was also no significant difference in the proportions of mothers with a family history of ATL, a divorce history, or particular screening test values or in the proportion of western blot-positive or -indeterminate individuals between the two groups.

In contrast, there were significant differences between the two groups regarding the feeding method that the participating

TABLE 1 The characteristics of HTLV-1-positive or HTLV-1-seroconverted pregnant women.

Characteristic	Mothers HTLV-1-positive at first pregnancy ($n = 133$)	Mothers seroconverted to HTLV-1-positive ($n = 9$)	*p*-Value
Age (year) at entry to APP Nagasaki			
Median (min, max), year	30 (17, 41)	31 (23, 38)	0.42
Age category, *n* (%)			
<25	19 (14.3)	2 (22.2)	
26–30	58 (43.6)	1 (11.1)	
31–35	44 (33.1)	5 (55.6)	
>36	12 (9.0)	1 (11.1)	
Nutrition method that participant mothers received from their mothers, *n* (%); [unknown = 22]			
Long-term breastfeeding	85 (63.9)	4 (44.4)	
Short-term breastfeeding	14 (10.5)	2 (22.2)	
Formula feeding	14 (10.5)	1 (11.1)	
Family history of ATL, *n* (%)			
Yes	9 (6.8)	1 (11.1)	
No	124 (93.2)	8 (88.9)	
Gravidity history, *n* (%); [unknown = 6]			
Once	61 (45.9)	0	
Twice	39 (29.3)	3 (15.8)	
Three or more	27 (20.3)	6 (31.6)	
Parity history, *n* (%); [unknown = 5]			
Once	76 (59.4)	0	
Twice	36 (28.1)	4 (44.4)	
Three or more	16 (12.5)	5 (55.6)	
Divorce history, *n* (%)			
Yes	10 (7.5)	1 (11.1)	
No	123 (92.5)	8 (88.9)	
Screening test values			
PA, titer	1,024 (16–8,192)	1,024 (16–8,193)	0.69
CLEIA, COI	34.4 (2.5–45)	34.4 (2.5–46)	0.47
WB test result, *n* (%); [unknown = 53]			
Positive	72 (90)	8 (88.9)	0.99
Indeterminate	8 (10)	1 (11.1)	
Quantified PVL, % per 1,000 PBMCs			
Median (min, max)	0.15 (0–7.05)	0.10 (0–1.09)	0.024

HTLV-1, human T-cell leukemia virus-1; APP, ATL Prevention Program; PA, particle agglutination; CLEIA, chemiluminescent enzyme immunoassay; COI, cutoff index; PVL, proviral load; PBMCs, peripheral blood mononuclear cells.

mothers themselves received from their mothers (i.e., the grandmothers), gravidity history, parity history, and HTLV-1 PVL. In brief, compared with the group of those already known to be HTLV-1-positive before pregnancy, the group of mothers that underwent HTLV-1 seroconversion between pregnancies had lower HTLV-1 PVL (0.15% vs. 0.10% per 100 PBMCs; $p < 0.024$).

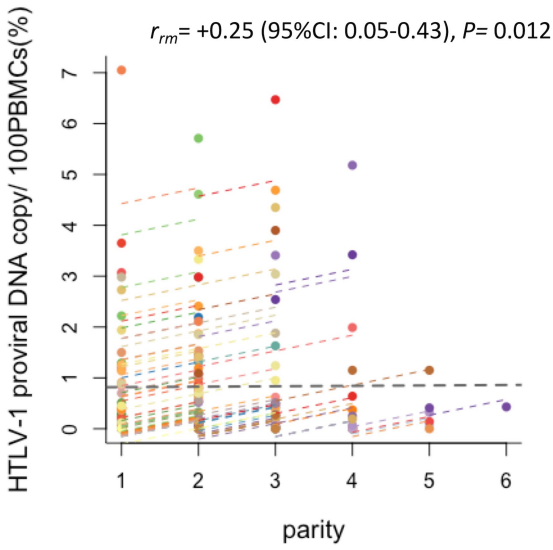

FIGURE 4
Changes in the HTLV-1 PVL of HTLV-1-positive pregnant women by parity. Plots of the correlation between the HTLV-1 PVL and parity of HTLV-1-positive pregnant women. Of the study participants, the 87 who were HTLV-1 seropositive and had their PVL measured more than twice were analyzed by repeated measures correlation (rmcorr). Each colored plot line shows the chronological change in HTLV-1 PVL of an individual HTLV-1-carrier pregnant woman. Positive correlations were found between increased HTLV-1 PVL and increased parity ($r = 0.25$, $p = 0.012$, 95% CI 0.05, 0.43).

Regarding whether the mothers had known about the HTLV-1 infection status of their husband or sexual partner, only two pregnant mothers reported HTLV-1 infection in their partner; the rest of the study participants did not know their partner's HTLV-1 infection status.

Sequential changes in the HTLV-1 PVL in HTLV-1-positive pregnant mothers

An analysis of the HTLV-1-positive mothers revealed a statistically significant positive correlation between an increase in parity number and an increase in HTLV-1 PVL ($rrm = +0.25$, $p = 0.012$; Figure 4).

Sequential changes in the HTLV-1 PVL In HTLV-1-seroconverted pregnant mothers

Among the nine HTLV-1-seroconverted pregnant mothers, there was only one mother (No. 2 in the Supplementary material S2) for whom the HTLV-1 PVL had been measured more than twice after HTLV-1 seroconversion. Her HTLV-1 PVL increased from 1.09 at her second delivery to 3.90 at her third delivery, which suggests that, even in

HTLV-1-seroconverted pregnant mothers, the HTLV-1 PVL increased over time.

Pregnancy outcomes

Table 2 summarizes the pregnancy outcomes of mothers of known HTLV-1-positive status and mothers that seroconverted to HTLV-1 between pregnancies. There was no statistically significant difference between the two groups in the frequency of any complications that occurred during pregnancy, the length of delivery time, or the sex distribution or birth weight of the babies.

Discussion

This is the first report on the HTLV-1-positive and -seroconversion status of pregnant mothers that participated in APP Nagasaki, and the first to report HTLV-1 PVL chronological data. Our main findings were that: (1) the proportion of those who underwent seroconversion from anti-HTLV-1 antibody negative to positive among pregnant mothers was 0.054%, with a seroconversion incidence rate of 17.5 per 100,000 person-years during the period 2011–2018, (2) HTLV-1 infection had no adverse effect on pregnancy outcomes in either the HTLV-1-infected or HTLV-1-seroconverted mothers; however, (3) the HTLV-1 PVL increased with increased parity number, and this showed a statistically significant positive correlation in both the HTLV-1-infected and the HTLV-1-seroconverted pregnant mothers.

TABLE 2 Pregnancy outcomes in mothers with known HTLV-1-positive status and mothers with HTLV-1 seroconversion during pregnancy.

Characteristic	Mothers HTLV-1-positive at first pregnancy ($n = 133$)	Mothers seroconverted to HTLV-1-positive ($n = 9$)	p-Value
No. of deliveries	265	10	–
Complications during pregnancy, *n* (%)			
No	222 (83.8%)	9 (90.0%)	0.67
Yes	43 (16.2%)	1 (10.0%)	
Length of delivery time, *n* (%)			
<34 weeks of gestation	222 (83.8%)	9 (90.0%)	0.37
34–36 weeks of gestation	11 (4.2%)	1 (10.0%)	
After 36 weeks of gestation	32 (12.1%)	0	
Sex of child, *n* (%)			
Unknown	7 (2.6%)	0	0.25
Male	130 (49.1%)	7 (70%)	
Female	128 (48.3%)	3 (30%)	
Birth weight, *n* (%)			
LFD	18 (6.8%)	1 (10.0%)	0.51
AFD	217 (81.9%)	9 (90.0%)	
HFD	30 (11.3%)	0	

LFD, light for dates; AFD, appropriate for dates; HFD, heavy for dates.

The estimated incidence rate (17.5 per 100,000 person-years) of HTLV-1 seroconversion among pregnant mothers aged 17–41 years in this analysis was higher than that for female blood donors aged 16–49 years (2.03–8.54 per 100,000 person-years) in Kyushu-Okinawa, where HTLV-1 is endemic (Satake et al., 2016), despite the similar age range of these groups. A possible explanation for this difference might be the eligibility criteria for blood donation, because pregnant women or recently postpartum mothers are not eligible to donate blood in Japan. Instead, the estimated crude incidence rate in this analysis was close to the HTLV-1 seroconversion rate in female repeated blood donors aged over 50 years in Kyushu-Okinawa (11.8–17.0 per 100,000 person-years; Satake et al., 2016). One possible explanation for the HTLV-1 seroconversion rate similarity in these two groups might be related to unprotected sexual contact with HTLV-1-infected partners—the majority of pregnant mothers in our study did not know the HTLV-1 infection status of their partner.

Regarding the PVL in HTLV-1-positive pregnant mothers, we previously reported that the PVL was the highest during the postpartum period (i.e., the period just after delivery) as compared with that during pregnancy terms (i.e., the first, second, and third trimesters; Fuchi et al., 2018). The present study supported the previous report by performing time-sequential analyses of the individual PVL of both HTLV-1-positive and HTLV-1-seroconverted pregnant mothers. In other words, we hypothesize that the positive correlation between the number of deliveries and HTLV-1 PVL found in this study indicates that the elevated HTLV-1 PVL that occurs during the first postpartum period is maintained and then the HTLV-1 PVL increases further during the second postpartum period. Thus, the individual HTLV-1 PVL increased with increased parity number among multiparous women (Figure 4). Alternatively, this finding could suggest that these women are continuously exposed to HTLV-1 from their HTLV-1-positive partners (Stuver et al., 1993; Sullivan et al., 1993; Kaplan et al., 1996). Therefore, they require regular medical check-ups and monitoring of the HTLV-1 PVL for the early detection of HTLV-1-associated diseases, not only by obstetric gynecologists, but also by hematologists. This is primarily because it has been well-established that the higher the PVL in HTLV-1-infected asymptomatic carriers, the higher their risk of developing HTLV-1-associated diseases (Nagai et al., 1998; Iwanaga et al., 2010), but also because a number of case reports have indicated the development of ATL in HTLV-1-positive pregnant mothers with a high PVL (Ohba et al., 1988; Utsumi et al., 1996; Safdar et al., 2002; Amor et al., 2013; Motedayen Aval et al., 2020; Ramassamy et al., 2020). In APP Nagasaki, one asymptomatic HTLV-1-positive pregnant woman developed ATL (Fuchi et al., 2016).

We also report here, for the first time, that even in a HTLV-1-seroconverted mother, the PVL increased between her second and third pregnancies with her increase in age (the second case in Supplementary material S2). This finding supports the idea that the HTLV-1 PVL increases with parity (or age) even in HTLV-1-seroconverted pregnant mothers. Therefore, we recommend that all HTLV-1-positive women of reproductive age be checked regularly for their HTLV-1 PVL and HTLV-1-associated diseases.

Regarding pregnancy complications in HTLV-1-positive pregnant mothers, previous studies reported no difference in the degree of pregnancy complications between those who were positive and those who were negative for anti-HTLV-1 antibody (Kusuhara et al., 1987; Rosadas et al., 2019). In the present study, among the 10 deliveries from nine HTLV-1-seroconverted pregnant mothers, only one baby (10% of all deliveries) was born prematurely at 29 weeks of gestation. Although only one premature case occurred, and therefore the sample size was small, the proportion (10%) was greater than the national average for premature cases (5.6%–5.7%) in Japan during 2015–2018 (Vital Statistics of Japan, 2015–2018). Further large-scale analyses are required to determine whether the occurrence of preterm/premature birth/delivery/labor is higher in HTLV-1-infected and/or HTLV-1-seroconverted pregnant mothers than in uninfected individuals.

Regarding the babies born from HTLV-1-positive mothers, Kusuhara et al. reported that such babies may acquire their own anti-HTLV-1 antibodies by the age of 3 years and continue to acquire such antibodies until the age of 18 (Kusuhara et al., 1987). Therefore, the obstetric gynecologists participating in APP Nagasaki advised each of the HTLV-1-positive mothers to have their children tested for HTLV-1 antibodies when they reach 3 years of age. In APP Nagasaki, 10 children were born from HTLV-1-seroconverted mothers; of these, one baby girl was given artificial nutrition and tested HTLV-1-negative, while no information was available on the other nine babies.

The major limitation of this study is that the findings were based on a single area of Nagasaki Prefecture; therefore, the results may not apply to other regions of Japan. Another limitation is that our analyses were based only on healthy pregnant women; as such, information on pregnant mothers with possible HTLV-1-associated diseases was lacking. Furthermore, our method was not capable of identifying cases in which a pregnant mother is HTLV-1-negative at the screening date but seroconverts to positive after the screening date. Therefore, our results might be an underestimation. Furthermore, we have little information on the HTLV-1-infection status of the partners of the pregnant mothers. Taking these limitations into account, the actual number of pregnant mothers horizontally infected with HTLV-1 might be higher than what we observed in this study. Also, since our APP project is a kind of a public-health project to avoid mother-to-child HTLV-1-transmission rather than a research-oriented project, the accuracy of data collection may not be perfect and only peripheral blood test and HTLV-1 PVL are regularly measured. Therefore, even if we are willing to perform a multivariate analysis, it is possible to include only factors such as age and the number of deliveries. However, since aging and the number of deliveries are almost proportional, therefore it is difficult to perform a multivariate analysis as another limitation of our study.

In conclusion, this is the first report on the individual change in HTLV-1 PVL of HTLV-1-positive and HTLV-1-seroconverted pregnant mothers and the infection status of their babies in APP Nagasaki. Although there were no serious adverse effects in the HTLV-1-infected pregnant mothers and their babies, we found that the HTLV-1 PVL of the mothers increased with parity (or age), which suggests that HTLV-1-infected women of reproductive age are continuously exposed to HTLV-1 horizontally from their HTLV-1-infected partners. Therefore, further careful follow-up is needed for both HTLV-1-positive pregnant mothers and their babies.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Institutional Review Board of Nagasaki University Hospital, Nagasaki, Japan (approval number: 20051810, September 2019). The patients/participants provided their written informed consent to participate in this study.

Author contributions

NK and NF analysis the data of HTLV-1 test among pregnant women. MI and KM organized the study protocol. NK, MI, and KM wrote the manuscript. YH, SM, NF, and KM collected the data of HTLV-1 tests among pregnant women. HM collected the data regarding Mother to Child transmission of HTLV-1. KY and KM performed the HTLV-1 screening test of pregnant women in Nagasaki. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmicb.2022.1036955/full#supplementary-material

References

Amor, M. M., Olaso, A. S., Atienza, R., Stueben, B., Cohen, S., Kossev, P., et al. (2013). Adult T-cell leukemia-lymphoma during pregnancy. *Case Rep. Oncol. Med.* 2013:631825. doi: 10.1155/2013/631825

Armstrong, M. J., Corbett, C., Rowe, I. A., Taylor, G. P., and Neuberger, J. M. (2012). HTLV-1 in solid-organ transplantation: current challenges and future management strategies. *Transplantation* 94, 1075–1084. doi: 10.1097/TP.0b013e318263ad7a

Bakdash, J. Z., and Marusich, L. R. (2017). Repeated measures correlation. *Front. Psychol.* 8:456. doi: 10.3389/fpsyg.2017.00456

Bangham, C. R. M. (2003). The immune control and cell-to-cell spread of human T-lymphotropic virus type 1. *J. Gen. Virol.* 84, 3177–3189. doi: 10.1099/vir.0.19334-0

Fuchi, N., Miura, K., Imaizumi, Y., Hasegawa, H., Yanagihara, K., Miyazaki, Y., et al. (2016). Adult T-cell leukemia-lymphoma in a pregnant woman diagnosed as a human T-cell lymphotropic virus type 1 carrier. *J. Obstet. Gynaecol. Res.* 42, 336–340. doi: 10.1111/jog.12904

Fuchi, N., Miura, K., Tsukiyama, T., Sasaki, D., Ishihara, K., Tsuruda, K., et al. (2018). Natural course of human T-cell leukemia virus type 1 proviral DNA levels in carriers during pregnancy. *J. Infect. Dis.* 217, 1383–1389. doi: 10.1093/infdis/jiy017

Gessain, A., and Cassar, O. (2012). Epidemiological aspects and world distribution of HTLV-1 infection. *Front. Microbiol.* 3:388. doi: 10.3389/fmicb.2012.00388

Hino, S. (2011). Establishment of the milk-borne transmission as a key factor for the peculiar endemicity of human T-lymphotropic virus type 1 (HTLV-1): the ATL prevention program Nagasaki. *Proc. Jpn. Acad. Ser. B Phys. Biol. Sci.* 87, 152–166. doi: 10.2183/pjab.87.152

Hino, S., Katamine, S., Miyata, H., Tsuji, Y., Yamabe, T., Miyamoto, T., et al. (1997). Primary prevention of HTLV-1 in Japan. *Leukemia* S3, 57–59.

Hino, S., Sugiyama, H., Doi, H., Ishimaru, T., Yamabe, T., Tsuji, Y., et al. (1987). Breaking the cycle of HTLV-I transmission via carrier mothers' milk. *Lancet* 2, 158–159. PMID: 2885619

Hino, S., Yamaguchi, K., Katamine, S., Sugiyama, H., Amagasaki, T., Kinoshita, K., et al. (1985). Mother-to-child transmission of human T-cell leukemia virus type-I. *Jpn. J. Cancer Res.* 76, 474–480. PMID: 2991060

Itabashi, K., Miyazawa, T., Sekizawa, A., Tokita, A., Saito, S., Moriuchi, H., et al. (2020). A nationwide antenatal human T-cell leukemia virus type-1 antibody screening in Japan. *Front. Microbiol.* 11:595. doi: 10.3389/fmicb.2020.00595

Iwanaga, M., Watanabe, T., Utsunomiya, A., Okayama, A., Uchimaru, K., Koh, K. R., et al. (2010). Human T-cell leukemia virus type I (HTLV-1) proviral load and disease progression in asymptomatic HTLV-1 carriers: a nationwide prospective study in Japan. *Blood* 116, 1211–1219. doi: 10.1182/blood-2009-12-257410

Kamihira, S., Dateki, N., Sugahara, K., Hayashi, T., Harasawa, H., Minami, S., et al. (2003). Significance of HTLV-1 proviral load quantification by real-time PCR as a surrogate marker for HTLV-1-infected cell count. *Clin. Lab. Haematol.* 25, 111–117. doi: 10.1046/j.1365-2257.2003.00503.x

Kaplan, J. E., Khabbaz, R. F., Murphy, E. L., Hermansen, S., Roberts, C., Lal, R., et al. (1996). Male-to-female transmission of human T-cell lymphotropic virus types I and II: association with viral load. The retrovirus epidemiology donor study group. *J. Acquir. Immune Defic. Syndr. Hum. Retrovirol.* 12, 193–201. doi: 10.1097/00042560-199606010-00014

Kashiwagi, K., Furusyo, N., Nakashima, H., Kubo, N., Kinukawa, N., Kashiwagi, S., et al. (2004). A decrease in mother-to-child transmission of human T lymphotropic virus type I (HTLV-I) in Okinawa, Japan. *Am. J. Trop. Med. Hyg.* 70, 158–163. doi: 10.4269/ajtmh.2004.70.158

Katamine, S. (1999). Milk-bone transmission of HTLV-1 and its intervention in Nagasaki. *Acta Med. Nagasaki* 44, 1–6.

Kinoshita, K., Hino, S., Amagasaki, T., Ikeda, S., Yamada, Y., Suzuyama, J., et al. (1984). Demonstration of adult T-cell leukemia virus antigen in milk from three sero-positive mothers. *Gan* 75, 103–105. PMID: 6329875

Kinoshita, K., Yamanouchi, K., Ikeda, S., Momita, S., Amagasaki, T., Soda, H., et al. (1985). Oral infection of a common marmoset with human T-cell leukemia virus type-I (HTLV-1) by inoculating fresh human milk of HTLV-1 carrier mothers. *Jpn. J. Cancer Res.* 76, 1147–1153. PMID: 3005206

Kuramitsu, M., Okuma, K., Yamochi, T., Sato, T., Sasaki, D., Hasegawa, H., et al. (2015). Standardization of quantitative PCR for human T-cell leukemia virus type 1 in Japan: a collaborative study. *J. Clin. Microbiol.* 53, 3485–3491. doi: 10.1128/JCM.01628-15

Kusuhara, K., Sonoda, S., Kazuo, T., Tokugawa, K., Fukushige, J., Ueda, K., et al. (1987). Mother-to-child transmission of human T-cell leukemia virus type 1 (HTLV-1): a fifteen-year follow-up study in Okinawa, Japan. *Int. J. Cancer* 40, 755–757. doi: 10.1002/ijc.2910400607

Matsuoka, M., and Jeang, K. T. (2007). Human T-cell leukaemia virus type 1 (HTLV-1) infectivity and cellular transformation. *Nat. Rev. Cancer* 7, 270–280. doi: 10.1038/nrc2111

Miura, K., and Masuzaki, H. (2017). "Prevention of human T-cell leukemia virus type 1 (HTLV-1) mother-to-child transmission" in *Adult T-cell Leukemia/Lymphoma*. Jpn. J. Obstet. Gynecol. Neonatal Hematol. (Japan: Springer), 157–169.

Moriuchi, H., Masuzaki, H., Doi, H., and Katamine, S. (2013). Mother-to-child transmission of human T-cell lymphotropic virus type 1. *Pediatr. Infect. Dis. J.* 32, 175–177. doi: 10.1097/INF.0b013e31827efc39

Motedayen Aval, L., Boullier, M., Lyall, H. P., Collins, G., Ayto, R. F., Kelly, D., et al. (2020). Adult T cell leukaemia/lymphoma (ATL) in pregnancy: a UK case series. *eJHaem* 2, 134–138. doi: 10.1002/jha2.142

Nagai, M., Usuku, K., Matsumoto, W., Kodama, D., Takenouchi, N., Moritoyo, T., et al. (1998). Analysis of HTLV-I proviral load in 202 HAM/TSP patients and 243 asymptomatic HTLV-I carriers: high proviral load strongly predisposes to HAM/TSP. *J. Neurovirol.* 4, 586–593. doi: 10.3109/13550289809114225

Ohba, T., Matsuo, I., Katabuchi, H., Nishimura, H., Fujisaki, S., Okamura, H., et al. (1988). Adult T-cell leukemia/lymphoma in pregnancy. *Obstet. Gynecol.* 72, 445–447.

Okochi, K., Sato, H., and Hinuma, Y. (1984). A retrospective study on transmission of adult T cell leukemia virus by blood transfusion: seroconversion in recipients. *Vox Sang.* 46, 245–253. doi: 10.1111/j.1423-0410.1984.tb00083.x

Paiva, A., Smid, J., Haziot, M. E. J., Assone, T., Pinheiro, S., Fonseca, L. A. M., et al. (2017). High risk of heterosexual transmission of human T-cell lymphotropic virus type 1 infection in Brazil. *J. Med. Virol.* 89, 1287–1294. doi: 10.1002/jmv.24745

Pique, C., and Jones, K. S. (2012). Pathways of cell-cell transmission of HTLV-1. *Front. Microbiol.* 3, 1–14. doi: 10.3389/fmicb.2012.00378

Ramassamy, J. L., Tortevoye, P., Ntab, B., Seve, B., Carles, G., Gaquière, D., et al. (2020). Adult T-cell leukemia/lymphoma incidence rate in French Guiana: a prospective cohort of women infected with HTLV-1. *Blood Adv.* 4, 2044–2048. doi: 10.1182/bloodadvances.2020001628

Rosadas, C., Tosswill, J. H., Tedder, R., and Taylor, G. P. (2019). Pregnancy does not adversely impact diagnostic tests for HTLV-1/2 infection. *PLoS Negl. Trop. Dis.* 13:e0007736. doi: 10.1371/journal.pntd.0007736

Roucoux, D. F., Wang, B., Smith, D., Nass, C. C., Smith, J., Hutching, S. T., et al. (2005). HTLV outcomes study investigators. A prospective study of sexual transmission of human T lymphotropic virus (HTLV)-I and HTLV-II. *J. Infect. Dis.* 191, 1490–1497. doi: 10.1086/429410

Safdar, A., Johnson, N., Gonzalez, F., and Busowski, J. D. (2002). Adult T-cell leukemia-lymphoma during pregnancy. *N. Engl. J. Med.* 346, 2014–2015. doi: 10.1056/NEJM200206203462519

Sasaki, D., Doi, Y., Hasegawa, H., Yanagihara, K., Tsukasaki, K., Iwanaga, M., et al. (2010). High human T cell leukemia virus type-1 (HTLV-1) provirus load in patients with HTLV-1 carriers complicated with HTLV-1-unrelated disorders. *Virol. J.* 7:81. doi: 10.1186/1743-422X-7-81

Satake, M., Iwanaga, M., Sagara, Y., Watanabe, T., Okuma, K., and Hamaguchi, I. (2016). Incidence of human T-lymphotropic virus 1 infection in adolescent and adult blood donors in Japan: a nationwide retrospective cohort analysis. *Lancet Infect. Dis.* 16, 1246–1254. doi: 10.1016/S1473-3099(16)30252-3

Satake, M., Yamaguchi, K., and Tadokoro, K. (2012). Current prevalence of HTLV-1 in Japan as determined by screening of blood donors. *J. Med. Virol.* 84, 327–335. doi: 10.1002/jmv.23181

Stuver, S. O., Tachibana, N., Okayama, A., Shioiri, S., Tsunetoshi, Y., Tsuda, K., et al. (1993). Heterosexual transmission of human T cell leukemia/lymphoma virus type I among married couples in southwestern Japan: an initial report from the Miyazaki cohort study. *J. Infect. Dis.* 167, 57–65. doi: 10.1093/infdis/167.1.57

Sullivan, K. M., and Dean, A. (2009). Open epi: a web-based epidemiologic and statistical calculator for public health. *Public Health Rep.* 124, 471–474. doi: 10.1177/003335490912400320

Sullivan, M. T., Williams, A. E., Fang, C. T., Notari, E. P., Poiesz, B. J., and Ehrlich, G. D. (1993). Human T-lymphotropic virus (HTLV) types I and II infection in sexual contacts and family members of blood donors who are seropositive for HTLV type I or II. American red Cross HTLV-I/II collaborative study group. *Transfusion* 33, 585–590. doi: 10.1046/j.1537-2995.1993.33793325055.x

Suzuki, S., Tanaka, M., Matsuda, H., Tsukahara, Y., Kuribayashi, Y., Gomibuchi, H., et al. (2014). Current status of HTLV-1 carrier in Japanese pregnant women. *J. Matern. Fetal Neonatal Med.* 27, 312–313. doi: 10.3109/14767058.2013.814631

Tajima, K., Tominaga, S., Suchi, T., Kawagoe, T., Komoda, H., Hinuma, Y., et al. (1982). Epidemiological analysis of the distribution of antibody to adult T-cell leukemia-virus-associated antigen: possible horizontal transmission of adult T-cell leukemia virus. *Gan* 73, 893–901. PMID: 6984401

Takahashi, K., Takezaki, T., Oki, T., Kawakami, K., Yashiki, S., Fujiyoshi, T., et al. (1991). Inhibitory effect of maternal antibody on mother-to-child transmission of human T-lymphotropic virus type I. the mother-to-child transmission study group. *Int. J. Cancer* 49, 673–677. doi: 10.1002/ijc.2910490508

Utsumi, T., Tsuda, A., Hirano, H., Goto, K., Tsubaki, H., and Tanaka, T. (1996). A case of pregnancy with adult T-cell leukemia. *J. Obstet. Gynaecol. Res.* 22, 599–601. doi: 10.1111/j.1447-0756.1996.tb01077.x

Vital Statistics of Japan (2015–2018). Ministry of internal affairs and communications Japan. e-Stat, Vital Statistics of Japan. Available at: https://www.e-stat.go.jp

Watanabe, T. (1997). HTLV-1-associated diseases. *Int. J. Hematol.* 66, 257–278.

Watanabe, T. (2011). Current status of HTLV-1 infection. *Int. J. Hematol.* 94, 430–434. doi: 10.1007/s12185-011-0934-4

World Health Organization (2020). Human T-lymphotropic virus type 1: technical report. Available at: https://apps.who.int/iris/handle/10665/339773 (Accessed March 3, 2021).

Yamanouchi, K., Kinoshita, K., Moriuchi, R., Katamine, S., Amagasaki, T., Ikeda, S., et al. (1985). Oral transmission of human T-cell leukemia virus type-I into a common marmoset (*Callithrix jacchus*) as an experimental model for milk-borne transmission. *Jpn. J. Cancer Res.* 76, 481–487.

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Review

How Can We Prevent Mother-to-Child Transmission of HTLV-1?

Kazuo Itabashi [1,*], Tokuo Miyazawa [2] and Kaoru Uchimaru [3,4]

1 Aiseikai-Memorial Ibaraki Welfare and Medical Center, Ibaraki 3100836, Japan
2 Department of Pediatrics, Showa University School of Medicine, Tokyo 1428666, Japan
3 Department of Hematology/Oncology, Research Hospital, The Institute of Medical Science, The University of Tokyo, Tokyo 1088639, Japan
4 Laboratory of Tumor Cell Biology, Department of Computational Biology and Medical Sciences, Graduate School of Frontier Sciences, The University of Tokyo, Tokyo 1088639, Japan
* Correspondence: kitaba@med.showa-u.ac.jp; Tel.: +81-29-353-7171

Abstract: The perception of human T-cell leukemia virus type 1 (HTlV-1) infection as a "silent disease" has recently given way to concern that its presence may be having a variety of effects. HTLV-1 is known to cause adult T-cell leukemia (ATL), an aggressive cancer of peripheral CD4 T cells; however, it is also responsible for HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Most patients develop ATL as a result of HTLV-1 mother-to-child transmission. The primary route of mother-to-child transmission is through the mother's milk. In the absence of effective drug therapy, total artificial nutrition such as exclusive formula feeding is a reliable means of preventing mother-to-child transmission after birth, except for a small percentage of prenatal infections. A recent study found that the rate of mother-to-child transmission with short-term breastfeeding (within 90 days) did not exceed that of total artificial nutrition. Because these preventive measures are in exchange for the benefits of breastfeeding, clinical applications of antiretroviral drugs and immunotherapy with vaccines and neutralizing antibodies are urgently needed.

Keywords: human T-cell leukemia virus type 1 (HTlV-1); adult T-cell leukemia (ATL); mother-to-child transmission; antenatal screening; prevention; nutritional regimens

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1. Introduction

There are seven known carcinogenic viruses: Epstein–Barr virus (EBV; also known as human herpesvirus 4 (HHV4)), hepatitis B virus (HBV), hepatitis C virus (HCV), human T-cell leukemia/lymphotropic virus type 1 (HTLV-1), human papilloma virus (HPV), Kaposi's sarcoma herpesvirus (KSHV; also known as human herpesvirus 8 (HHV8)), and Merkel cell polyomavirus (MCV). These viruses are responsible for approximately 15% of all human cancers [1]. Among these viruses, HTLV-1 was the first retrovirus discovered to be carcinogenic [2,3], and the patients showed unique clinical characteristics. HTLV-1 is known to cause adult T-cell leukemia (ATL), an aggressive cancer of peripheral CD4 T cells; however, it is also responsible for HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) [4,5]. HTLV-1 carriers have an estimated lifetime risk of 2–5% for the development of ATL [6] and 0.25–1.8% for HAM/TSP [7,8]. Both diseases exhibit serious clinical manifestations and poor prognosis despite therapeutic efforts. In addition to these two diseases, HTLV-1-associated uveitis is widely known [9]. Although ATL and HAM/TSP have been recognized as major outcomes of HTLV-1 infection, they account for less than 10% of the infected population. A recent meta-analysis showed that disease outcomes (morbidity and mortality) for which HTLV-1 is not a necessary diagnostic criterion are clearly associated with HTLV-1 infection (10). This analysis showed a 57% increased risk of early mortality, independent of ATL or HAM/TSP. As ATL and HAM/TSP are present in less than 10% of cases, increased mortality cannot be explained by these two diseases alone [10]. Thus, HTLV-1 infection is likely to affect human health in more ways than currently known and is a global burden [11,12].

Although not ubiquitous, HTLV-1 is found worldwide, and clusters of high endemicity often exist near areas where the virus is rarely present. This could be explained by factors including a possible founder effect, predominance of mother-to-child transmission (MTCT), and cell-to-cell transmission mechanisms [13,14]. The estimated number of HTLV-1 carriers is 5–10 million people across the world [13]. This number may be underestimated because it does not include Russia, China, and India, countries with large populations. The most endemic regions are the southwestern part of Japan, sub-Saharan Africa, South America, the Caribbean region, and foci in the Middle East and Australo-Melanesia regions [13]. HTLV-1-infected individuals are often asymptomatic. Therefore, there is concern about the silent spread of mother-to-child and horizontal transmission.

Most ATL cases are attributed to MTCT [15,16]. The MTCT rate is estimated to be approximately 20% [11], and if we assume a 5% lifetime risk of developing ATL, it is estimated that 25% of cases of MTCT are at a risk of developing ATL. HTLV-1 is a latent virus. Because the host immune system cannot eliminate the virus, HTLV-1 persists in the host and poses a lifelong threat of the development of ATL, HAM/TSP, and other diseases [10,17]. Currently, there is no effective antiretroviral therapy (ART) in clinical use, and the only available measure is the prevention of infection. In this article, we review how HTLV-1 MTCT can be prevented and discuss the challenges in prevention measures.

2. Mechanisms of HTLV-1 Transmission

2.1. Cell-to-Cell Transmission

HTLV-1 virions are rarely detected in the extracellular environment [18]. Thus, HTLV-1 infection is believed to spread predominantly through direct cell-to-cell contact. Cell-to-cell transmission may enhance the multiplicity of infection and evade the host immune responses. It also aids rapid viral replication kinetics by directing virus assembly and budding to sites of cell-to-cell contact [19,20]. Although in vivo evidence has not been established yet, in vitro studies have suggested that HTLV-1 cell-to-cell transmission may occur through viral synapses [21], conduits [22], biofilm-like structures [23], and extracellular vesicles [24]. Recently, Hiyoshi et al. [25] reported that the host factor M-Sec, which induces membrane protrusion and establishes intercellular conduits, plays an important role in efficient viral infection. These modes seem to be favorable for the virus to escape immune elimination (HTLV-1-specific T-cell unresponsiveness) and efficiently reach contacted cells, resulting in increased proviral load (PVL) [26]. HTLV-1 predominantly infects CD4+ T cells via cellular receptors such as heparin sulfate (HS) proteoglycans and neuropilin 1 (NRP-1), which help in initial binding to the cell and glucose transporter 1 (GLUT1) [27–31].

Recent studies have shown that cell-free HTLV-1 can infect certain types of cells rather than being poorly infectious as previously thought [27]. In vitro studies have shown that HTLV-1 infection of T cells via dendritic cells (DCs) can occur in two different ways: In cis-infection, after infecting DCs, de novo produced HTLV-1 is transferred to T cells [32]. In trans-infection, uninfected DCs capture the virus produced by infected T cells and transfer it to T cells before becoming infected [32–34].

Because DCs, monocytes, epithelial cells, macrophages, and B cells express these receptors, they can also infect each other in individuals with HTLV-1 infection [27,35]. CD4+ T cells are the primary targets of HTLV-1 infection in vivo [36]. In addition, HTLV-1 proviral DNA can be detected in CD8+ T cells [37], DCs [38], plasmacytoid dendritic cells [39], and monocytes, including macrophages [35,40], albeit to a lesser extent.

2.2. HTLV-1 Life Cycle

Infected lymphocytes transmit HTLV-1 through intercellular contact with target cells, and viral components, including the single-stranded RNA genome of HTLV-1, are transferred to target cells through these junctions [41]. HTLV-1 genomic RNA (gRNA) is reverse-transcribed in the cytoplasm of target cells, resulting in double-stranded DNA of size 9 kb, which is inserted into the host genome in the target cell nucleus to form a provirus. The position at which the double-stranded DNA is inserted is not completely random. HTLV-1

is preferentially incorporated into characteristic regions; however, the underlying mechanism is currently unknown [42,43]. The provirus is transcribed by RNA polymerase II in the cell and is modified post-transcriptionally. Both full-length and spliced viral mRNAs are transported from the nucleus to the cytoplasm. Viral proteins are then translated by the translation machinery of the host cell, and Gag, Gag-Pol, and Env proteins are transported to the plasma membrane along with two copies of HTLV-1 gRNA. Immature viral particles are formed from these viral proteins and gRNAs, which release from the cell surface. Subsequently, viral proteases act on immature viral particles to form mature viral particles with infectious potential (see Martin's review [44] for a detailed description of this process).

2.3. HTLV-1 Replication

According to previous studies, immediately after infecting the cell, the HTLV-1 virus spreads from cell to cell. Later, during the chronic infection phase, the virus survives through clonal expansion as a provirus, which is incorporated into the host cell genome and replicates as the infected cells divide [27,45]. Replication of HTLV-1 occurs via (i) an infection cycle involving viral budding and infection of new target cells and (ii) mitosis of cells harboring an integrated provirus [46]. During HTLV-1 integration into the host genome, the 5′ and 3′ ends of HTLV-1 are duplicated to form long terminal repeats (LTRs). These regions constitute the promoter regions as transcription factor binding sites. The proviral genome comprises the structural genes gag, pol, and env flanked by LTR at both ends. The genome also contains the pX region, which has four partially overlapping open reading frames encoding p12, p13, p30, Rex, and Tax, which are regulatory or accessory proteins. The viral genes are transcribed from the 5′ LTR. HTLV-1 also expresses a minus-stranded RNA that encodes HTLV-1 bZIP factor (HBZ), a basic leucine zipper factor protein. *HBZ* is the only gene that is encoded in the antisense strand and is transcribed from the 3′ LTR. The HTLV-1 genome has the potential to express multiple products using various strategies, such as frameshifting and alternative mRNA splicing.

Tax and *Rex* are essential for viral replication. *Tax* promotes viral mRNA synthesis by transactivating the HTLV-1 promoter located in the 5′ LTR. Tax acts in a coordinated manner on various intracellular targets during cell transformation and is involved in immortalization, cell proliferation, and leukemogenesis. On the other hand, Tax is a major target antigen recognized by cytotoxic T lymphocytes (CTLs) [47]. Therefore, for HTLV-1-infected cells to survive, *Tax* expression must be tightly regulated to evade host immune surveillance. Tax expression is normally suppressed to escape CTLs, but at the same time Tax is transiently expressed to maintain and expand HTLV-1-infected cells [48]. The *HBZ* gene is the only HTLV-1 gene present in all infected individuals. Unlike Tax, HBZ is always expressed but is less immunogenic, and thus more likely to escape CTL clearance. Furthermore, HBZ may suppress the effects of Tax, leading to survival of infected cells and oncogenesis [49]. *Rex* regulates the synthesis of structural proteins at the post-transcriptional level [50]. The accessory proteins p12/p8, p13, and p30 are important for viral infectivity and persistence in vivo but are not essential for viral replication in vitro [51–53].

3. Modes of HTLV-1 Transmission

There are two modes of HTLV-1 transmission: horizontal infection and antenatal or postnatal MTCT [15,54]. In 2013, there were an estimated 1780 pregnant carriers in Japan [55]. In addition, the MTCT rate in a recent prospective cohort study in Japan was observed as 4.5% (95% confidence interval (C.I.) 2.6–7.4%) [56]. Based on these data, the number of new mother-to-child infections is estimated to be 70 (95% C.I. 41–115) per year. The number of new horizontal infections in Japan is estimated to be approximately 4000 per year, which is far larger than the number of new infections caused by MTCT.

3.1. Horizontal Transmission

The main sources of horizontal infection are sexual intercourse, blood transfusion, and parenteral transmission via contaminated needles. According to the WHO Technical

Report, 23 countries have implemented mandatory screening for HTLV-1 antibodies in all donated blood samples. However, despite being mandatory, HTLV-1 antibody screening is not always performed during blood donations by the same person in these countries [11]. Since donor blood screening for HTLV-1 infection is always performed at the time of blood collection [57], horizontal infection occurs mainly through sexual transmission in Japan [58]. Organ transplantation from an HTLV-1 carrier has also been identified as a cause of horizontal HTLV-1 infection, and the addition of HTLV-1 antibody testing to donor testing has been advocated [59].

The Miyazaki Cohort Study examined heterosexual HTLV-1 transmission in 534 couples over a five-year period from 1984 to 1989. This study showed that the infection rate was 3.9 times higher when the carrier spouse was male [60]. Satake et al. evaluated 3,375,821 repeat blood donors aged 16–69 years for new HTLV-1 infection over a 4.5-year period. Their results were as follows [58]: (i) at least 4000 adolescents and adults were estimated to be newly infected each year, (ii) the incidence density was significantly higher in women (6.88 per 100,000 person-years; 95% C.I. 6.17–7.66) than in men (2.29 per 100,000 person-years; 95% C.I. 1.99–2.62; $p < 0.0001$), (iii) the highest number of newly infected individuals were males in their 60s and females in their 50s, regardless of endemic area, (iv) a higher number of males in their 20s were newly infected in metropolitan areas (non-endemic areas) than in non-endemic areas. As new infections in adolescence and adulthood are primarily caused by sexual transmission in Japan, reports advocate the importance of preventing horizontal transmission from a public health perspective.

Factors related to sexual intercourse include non-use of contraceptives, numerous partners, and male-to-male intercourse [61]. Kaplan et al. found that high PVL and length of relationship played a role in viral transmission from male carriers to non-carrier women [7]. A higher PVL tends to be associated with HAM/TSP [62], ATL [63], HTLV-1-associated infectious dermatitis [64], and HTLV-1 uveitis [65]. In addition, PVL tends to be higher in patients co-infected with *Strongyloides stercoralis* than in the others [66]. Sexual transmission occurs more efficiently from men to women than women to men and might be enhanced by sexually transmitted diseases that cause ulcers and result in mucosal ruptures, such as syphilis, herpes simplex type 2 (HSV-2), and chancroid [67]. Other sexually transmitted diseases may result in the recruitment of inflammatory cells and increase the risk of HTLV-1 acquisition and transmission [61].

3.2. Mother-to-Child Transmission

The main reason for the focus on MTCT of HTLV-1 is that most ATL cases originate from MTCT [64], and ATL rarely develops in individuals infected during adulthood [6].

3.2.1. Transmission Routes of MTCT

The Nagasaki ATL Prevention Program found that exclusive formula feeding (ExFF) markedly reduced the HTLV-1 MTCT rate from 20.3% to 2.5% [68]. Accumulating evidence has shown that the HTLV-1 MTCT rate in children who were exclusively fed infant formula was significantly lower than in children who were breastfed for an extended period [68–71]. Therefore, the primary route of MTCT is through breastfeeding. However, MTCT has been observed in a small percentage of children (approximately 2.5–6.7%) exclusively fed infant formula [56,68,71]. This suggests the possibility of antenatal MTCT [54].

Antenatal Transmission

The presumed pathways for antenatal MTCT are intrauterine and the birth canal. A recent study showed that trophoblasts in pregnant carriers are highly susceptible to HTLV-1, suggesting that intrauterine infection may occur due to impairment of the blood–placental barrier [72]. However, there is little clinical evidence for intrauterine ascending infection, intrapartum infection due to exposure to contaminated maternal blood, or intrauterine infection [51].

Transmission through Breastfeeding

It is unclear which infected cells in breast milk are transmitted to the infant and how MTCT is established. It has been noted that viral uptake during lactation may occur in the tonsillar mucosa, the intestinal mucosa, or both sites [73], while postnatal infection is thought to occur when infected cells in ingested breast milk enter the infant's digestive tract [74,75]. The number of leukocytes in breast milk decreases to 0–2% of the total cell count within a few weeks of lactation. In addition to leukocytes, many other cell types are present in breast milk, including mammary luminal epithelial cells, mammary gland cells, and stem/progenitor breast cells, which vary with lactation period, maternal conditions, and infant feeding [76]. HTLV-1 MTCT has been thought to be primarily mediated by CD4+ T cells, but several studies have suggested that mammary epithelial cells and macrophages may be involved in the persistence and spread of HTLV-1 infection from the carrier mother [77–79]. However, it remains unclear which cells present in breast milk are the main players in breast milk infection. The process from the contact of infected cells with the mucosa to the spread of infection in the submucosal tissue has been described in detail in several reviews [27,46,80], and the following process has been postulated by Carpenter et al. [46]: (i) bilions incorporated into vesicles migrate from the apical surface of epithelial cells to the basal surface of the epithelial cell [73], (ii) newly produced virions are released from the basal surface of infected epithelial cells [80], (iii) HTLV-1-infected cells are bypassed through the injured mucosa [81], and (iv) macrophages pass through the epithelium, as seen with HIV [82]. The process by which infected cells in breast milk enter the infant's gastrointestinal tract and establish infection is not yet fully understood.

3.2.2. Risk Factors Associated with MTCT

Since the 1980s, it has been widely recognized that extended breastfeeding is a risk factor for MTCT, and as discussed below, avoidance of breastfeeding is an important measure for preventing MTCT [71,83]. However, the involvement of other factors should be considered when testing pregnant women, particularly in countries or regions where maternal HTLV-1 antibody screening is not routinely performed [84]. Furthermore, even if HTLV-1 screening tests are performed on all pregnant women, as in Japan [83], intervention measures considering the risk factors are desirable to minimize avoidance of breastfeeding. The risk factors for MTCT reported to date are shown in Figure 1. However, sensitivity and specificity of these factors, except the duration of breastfeeding, in predicting MTCT have not been sufficiently studied. Plancoulaine et al. detected chromosome 6q27 as the dominant gene that predisposes individuals to HTLV-I infection based on a large genetic epidemiological study on an HTLV-1 endemic population of African descent living in French Guiana [85–87].

There has long been an interest in whether the presence or transfer of antibodies in breast milk plays an effective role in preventing MTCT. Moreover, it has been reported that pregnant women infected with HTLV-1 have significantly increased levels of anti-HTLV-1 antibodies, although their PVL did not change during pregnancy [88]. This results in the transmission of more antibodies to the fetus through the placenta during pregnancy. This report is consistent with the hypothesis that infection may be prevented in fetuses and early postnatal infants.

Rosadas et al. measured anti-HTLV-1/2 IgG antibodies and PVL in paired blood and breast milk from HTLV-1/2-positive mothers and reported that HTLV-1 PVL and IgG binding ratios were similar in plasma and breast milk; however, the anti-HTLV-1/2 IgG antibody titer in plasma was approximately 1000 times higher than that in breast milk [89]. After delivery, HTLV PVL increased in the mother's blood [90]. Given the antepartum and postpartum changes in PVL and antibodies in infected mothers, as well as the lower antibody levels in breast milk, MTCT prevention with short-term breastfeeding (discussed below) may be less likely to involve IgG antibodies in breast milk. One reason for the increased risk of MTCT with prolonged breastfeeding may be related to lower levels of transitional antibodies during infancy and increased cumulative intake of infected cells

ingested through breast milk. High maternal PVL has also been identified as a risk factor for MTCT [91,92]. This was also reflected in elevated maternal antibody titers [93].

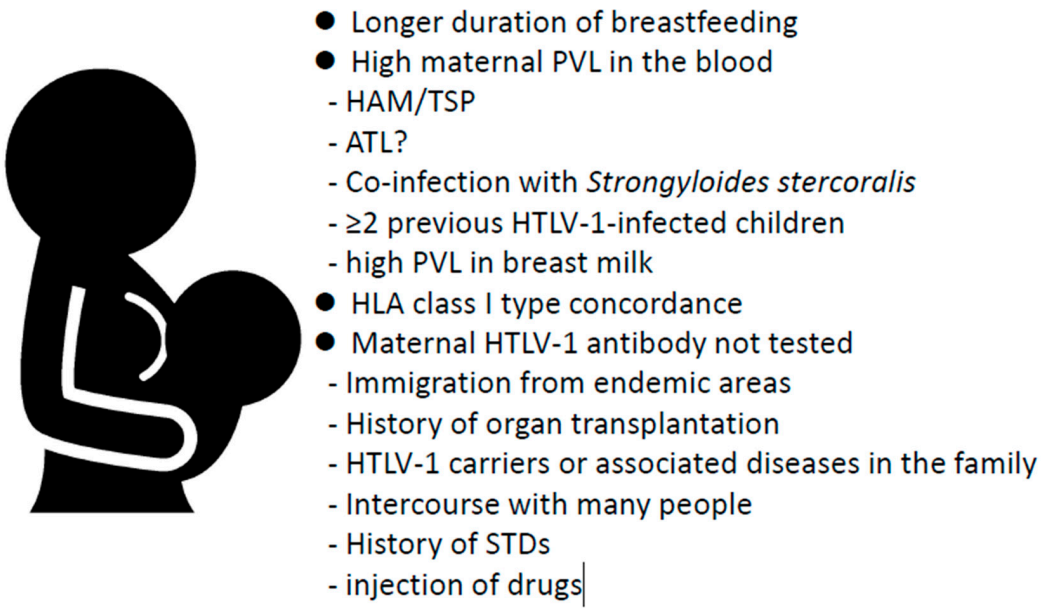

Figure 1. Risk factors associated with development of HTLV-1 mother-to-child transmission. Risk factors for mother-to-child transmission are broadly classified as long-term breastfeeding, high PVL in carrier mothers, HLA class type 1 concordance between mother and child, and mothers with untested HTLV-1 antibodies. HLA, human leukocyte antigen.

Other risk factors for carrier mothers include HAM/TSP complications [94], co-infection with *Strongyloides stercoralis* [94], ≥2 previous children with HTLV-1 infection [91], high PVL in breast milk [95], and human leukocyte antigen (HLA) class I type concordance between mother and child via breastfeeding [96]. Furthermore, in mothers with untested HTLV-1 antibodies from endemic areas, a lack of effective intervention may result in MTCT.

Substances present in breast milk, such as tumor growth factor (TGF)-β and lactoferrin, which are abundant in colostrum [92,97], promote HTLV-I replication [98,99]. Furthermore, lactoferrin expression has been shown to be elevated during HTLV-1 infection [100]. However, the levels of these components are not constant during lactation and vary from person to person. Therefore, it is unclear how they affect MTCT.

4. Strategies to Prevent HTLV-1 MTCT

Theoretical strategies to prevent the MTCT of HTLV-1 include avoidance of breastfeeding, reduction in infected cells in breast milk, and administration of vaccines, neutralizing antibodies, and antiretroviral drugs. These strategies are discussed in the following sections. Other important strategies include promoting the use of condoms to prevent transmission to uninfected women from male carriers. Furthermore, it is essential to disseminate knowledge about HTLV-1 infection not only to medical providers and health administrators but also to the general public.

4.1. Prevention of MTCT through Nutritional Regimens

Several nutritional regimens have been proposed to prevent the MTCT of HTLV-1 (Table 1) [54]. However, some methods provide limited evidence. Previous epidemiological and animal studies have shown that most HTLV-1 MTCT occurs through breast milk containing infected cells. Therefore, ExFF, which intercepts breast milk containing infected cells, is theoretically the most reliable method for postnatal prevention. As mentioned

above, a follow-up study by the ATL Prevention Program (APP), which started in 1987 in the Nagasaki Prefecture, showed that ExFF reduced the rate of MTCT to approximately 1/10 of that after long-term breastfeeding (≥6 months) [68]. However, it has been suggested that the longer a carrier mother breastfeeds her infant, the higher the MTCT rate [91].

Table 1. Effectiveness of feeding regimens in peventing mother-to-child transmission and their limitations.

Nutritional Regimens	Effectiveness on MTCT	Comments
Exclusive infant formula feeding (ExFF)	Widely used and well evaluated to block MTCT through breast milk	Prevents about 95% or more of MTCT No benefits from breastfeeding Concerns about increased risk of postpartum depression and impaired mother–child bonding
Short-term breastfeeding (≤3 months)	No apparent difference in the MTCT prevention effect (vs. ExFF) Majority of studies in Japan	Acquisition of some benefits of breastfeeding Approximately 18% of children exceed 4 months of breastfeeding Need to provide adequate support for weaning No data on the preventive effect of postpartum depression or impairment of mother–child bonding
Short-term breastfeeding (≤6 months)	Approximately three times increased risk of MTCT (vs. ExFF)	Better to avoid this regimen
Frozen–thawed breast milk feeding	No apparent difference in the MTCT prevention effect (vs. ExFF) Only three small case studies in Japan, with little confidence in preventive effects	Time-consuming Considered for use in infants admitted in the NICU No data on the preventive effect of postpartum depression or impairment of mother–child bonding
Mixed feeding	Unknown effectiveness of MTCT prevention due to lack of data (vs. ExFF)	Concerns about increased risk of MTCT due to damage to the intestinal mucosa Better to avoid this regimen
Banked human milk pasteurization	No data available, but expected to be as effective as ExFF in preventing MTCT	No use of breast milk from untested HTLV-1 donors No data on the preventive effect of postpartum depression or impairment of mother–child bonding

Note: It should be noted that ~5% of antenatal infections cannot be avoided regardless of which nutritional regimen is chosen. MTCT, mother-to-child transmission; NICU, neonatal intensive care unit. The table is reproduced from Itabashi et al. [54] with some modifications.

In Japan, methods such as limiting the duration of breastfeeding to three to six months or inactivating infected cells by freezing and thawing procedures (frozen–thawed breast milk feeding; FTBMF) have been proposed as alternatives to ExFF for carrier mothers who wish to breastfeed their babies [83]. In the Kagoshima Prefecture, an endemic area of Japan, short-term breastfeeding (STBF) has historically been promoted if mothers wish to breastfeed, and over 60% of mothers have opted for STBF [101]. This indicates that a significant number of HTLV-1 carrier mothers wished to breastfeed their infants. However, because the effectiveness of these interventions in preventing MTCT is based on small observational studies rather than randomized controlled trials, sufficient evidence is lacking.

In a recent technical report on HTLV-1, the WHO recommends that "available data should be further analyzed to better define the risk of HTLV-1 transmission associated with specific duration of breastfeeding, balanced with the risks of other adverse health outcomes that may result from reduced breastfeeding" [102]. In this context, Itabashi et al. conducted a prospective multicenter cohort study involving HTLV-1 carrier pregnant women and their infants as part of the Health, Labor, and Welfare Science Research Program in Japan

to determine the rate of MTCT by ExFF, STBF, and FTBMF [56]. Miyazawa et al. reported findings through a systematic review that integrated the results of the cohort study and previous studies [103].

4.1.1. Exclusive Formula Feeding (ExFF)

A meta-analysis of 12 studies by Rosadas et al. in 2022 showed that the risk of MTCT with breastfeeding (of any duration) was approximately four times higher than that with ExFF [84], supporting the effectiveness of avoiding breastfeeding for the prevention of infection. However, ExFF lacks the various positive effects of breastfeeding, such as nutritional and immunological benefits, long-term disease prevention, economic efficiency, promotion of mother–infant bonding, and promotion of maternal recovery after delivery. Many HTLV-1 carrier mothers are concerned that they cannot form mother–infant bonds because they cannot breastfeed their babies [104].

According to a review article by Millen et al., avoidance of breastfeeding is not an option in resource-limited areas or populations with few infected individuals [105]. In particular, in developing countries with high morbidity and mortality rates of serious gastrointestinal and other infections due to poor sanitation, which do not provide a stable supply of formula, baby bottles, and clean water, the advantages of the immunological benefits of breast milk may outweigh the disadvantages of the MTCT of HTLV-1. Therefore, the recommended level of breastfeeding avoidance to prevent HTLV-1 MTCT should be considered based on each local situation.

4.1.2. Short-Term Breastfeeding (STBF)

Although the precise mechanism of MTCT prevention by STBF is unknown, it is assumed to be due to the transplacental transfer of neutralizing antibodies from the mother to infant during pregnancy. The antibodies remain in the infant for several months after birth and may prevent MTCT during the first few months of life. The period of exposure to the infected cells is short, and the cumulative number of infected cells entering the digestive tract is small.

In the Nagasaki Prefecture, the duration of STBF has been set at six months or less since the late 1980s. During this period, the MTCT rate was 2.4% (23/962) for ExFF, while it was significantly higher for STBF ($\leq$6 months) at 8.3% (14/169) [106]. Since the late 1990s, when the duration of STBF was changed to three months or less, the MTCT rate was observed to be 3.7% (8/218) for ExFF versus 2.8% (1/36) for STBF, with no statistical difference between the two [106]. In the Kagoshima Prefecture, between 1986 and 2006, the MTCT rate for ExFF was 4.8% (16/331), whereas that for STBF ($\leq$3 months) was 1.6% (2/126) [107]. Based on these results, the recommended period of STBF is less than three months (less than 90 days after birth) in Japan [54].

In a Japanese prospective cohort study by Itabashi et al., the intention-to-treat (ITT) analysis showed that the MTCT rates for STBF (less than 90 days) and ExFF were 2.3% (4/172 children born to carrier mothers) and 6.4% (7/110), respectively, with no statistically significant difference between the two groups [56]. Among 172 mother–infant pairs who chose STBF, 33.5% were still breastfeeding at three months of age and 7.8% at six months, and the approximate formula suggests that 18.2% were still breastfeeding at 4 months of age [56]. Thus, even if a mother chooses STBF, it is difficult for her to terminate breastfeeding and make the transition to ExFF within $\leq$3 months (90 days) of age of the infant. In addition, there is a concern that prolonged breastfeeding may increase the risk of MTCT.

A 2021 systematic review included a meta-analysis of the risk of MTCT of STBF $\leq$ 3 months and STBF $\leq$ 6 months compared with that of ExFF [103]. The meta-analysis integrated five retrospective studies and the cohort study by Itabashi et al.; comparing STBF $\leq$ 3 months (including <90 days) with ExFF found no statistical difference in the risk of MTCT between the two groups (pooled risk ratio (RR): 0.72, 95% CI: 0.30–1.77) (Figure 2) [103]. In contrast, a meta-analysis integrating five retrospective studies and comparing STBF $\leq$ 6 months and ExFF showed that STBF $\leq$ 6 months was associated with an approximately 3-fold higher risk

of MTCT than that of ExFF (pooled RR: 2.91, 95% CI: 1.69–5.03) (Figure 3) [103]. Although there was no statistical difference in the MTCT rates between STBF ≤ 3 months and ExFF, Rosadas et al. documented that all studies included in the meta-analysis were observational studies in Japan [84].

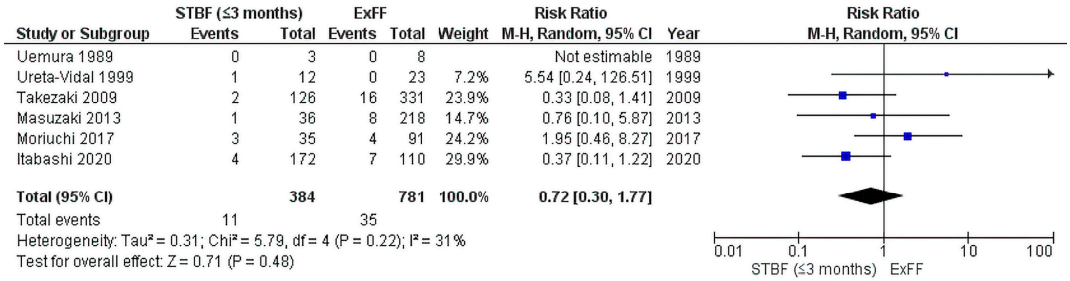

Figure 2. Forest plot of the risk ratios of HTLV-1 MTCT in the STBF ≤ 3 months group compared with that of the ExFF group. There is no statistical difference in the risk of MTCT between the two groups (pooled risk ratio (RR): 0.72, 95% CI: 0.30–1.77). Abbreviations: STBF, short-term breastfeeding; ExFF, exclusive formula feeding; M–H, Mantel–Haenszel; CI, confidence interval; RR, risk ratio; MTCT, mother-to-child transmission; events, number of cases with mother-to-child transmission; total, number of children born to carrier mothers; weight, influence of studies on overall meta-analysis. The figure is reproduced from Miyazawa et al. [103].

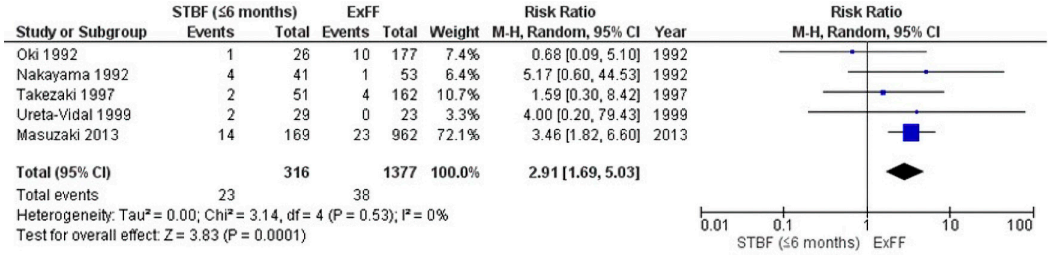

Figure 3. Forest plot of the risk ratios of HTLV-1 MTCT in the STBF ≤ 6 months group compared with that of the ExFF group. Comparing STBF ≤ 6 months and ExFF showed that STBF ≤ 6 months was associated with an approximately 3-fold higher risk of MTCT than that of ExFF (pooled RR: 2.91, 95% CI: 1.69–5.03). Abbreviations: STBF, short-term breastfeeding; ExFF, exclusive formula feeding; M–H, Mantel–Haenszel; CI, confidence interval; RR, risk ratio; MTCT, mother-to-child transmission; events, number of cases with mother-to-child transmission; total, number of children born to carrier mothers; weight, influence of studies on overall meta-analysis. The figure is reproduced from Miyazawa et al. [103].

4.1.3. Frozen–Thawed Breast Milk Feeding (FTBMF)

It is speculated that freeze–thaw treatment of breast milk destroys infected cells, thereby inactivating its infectivity in the infant [54]. Specifically, the expressed breast milk is frozen in a home freezer at −20°C or lower for at least 24 h, thawed, and fed to the infant. Milk expression, freezing, and thawing are necessary and time-consuming processes. In a Japanese prospective cohort study, only 19 of 313 mothers opted for FTBMF, and MTCT was confirmed in one infant [56]. A meta-analysis integrating three prospective observational studies, including the cohort study by Itabashi et al., found no difference in the risk of MTCT between ExFF and FTBMF (pooled RR: 1.14, 95% CI: 0.20–6.50) [103]. However, the number of cases analyzed was small, the subjects were limited to Japan, and the duration of FTBMF was not constant, and included cases of a short duration (2–6 months) [108,109]. Therefore, it may be premature to conclude that FTBMF is an effective intervention to prevent MTCT. However, FTBMF is routinely administered to preterm infants born at less than 32 weeks of gestation who are at risk for infection, necrotizing enterocolitis, and

related deaths [110]. Thus, FTBMF would outweigh the risk of HTLV-1 MTCT while in the neonatal intensive care unit (NICU) for such infants.

FTBMF requires several work processes. If an infant born to an infected mother is admitted to the NICU, the mother's work involves expressing and freezing breast milk, and then bringing the frozen breast milk to the NICU. However, if not admitted to the NICU, two additional processes are required: thawing the frozen breast milk and transferring it to a bottle. It is difficult to repeat a series of work processes on a daily basis.

4.1.4. Milk Pasteurization and Banked Human Milk

When newborn infants cannot be fed with their mother's milk, such as preterm infants admitted to the NICU, human milk donated to human milk banks is an important resource for supporting their health. According to international guidelines [111], milk is pasteurized using the Holder method (62.5 °C for 30 min). According to a systematic review conducted by Pitino et al., all viruses studied, except parvoviruses, are susceptible to thermal killing [112]. Unfortunately, this review did not report any studies on HTLV-1. Yamato et al. reported that heat treatment (56°C for 30 min) eliminated HTLV-1 activity in an in vitro study [113], but no subsequent clinical studies have been conducted to date. Theoretically, this is sufficient to suppress transmission of infection through breastfeeding; however, further studies are required to clarify this issue.

Banked human milk should be screened for maternal HTLV-1 infections [114]. Theoretically, banked human milk could have the same preventive effect as ExFF in infants born to HTLV-1 carriers. However, while banked human milk may provide some health benefits for infants and children [115], it is unlikely to reduce carrier mothers' anxiety and/or impairment of mother–child bonding. This method would be available assuming that resources are abundant and a breast milk banking system exists; however, clinical studies must be conducted before this can be performed.

4.1.5. Mixed Feeding

The method of supplementing the deficiency with infant formula in the case of decreased breast milk secretion is called mixed feeding. Some carrier mothers intentionally choose mixed feeding immediately after birth to reduce the amount of breast milk ingested by their infants, thus reducing the amount of virus transferred to them. However, the effect of this approach on MTCT is unknown. In recent studies, the rate of MTCT of HIV was extremely high (approximately 20%) compared to normal breastfeeding or infant formula feeding [116]. Mixed feeding may cause gastrointestinal mucosal injury or dysbiosis, resulting in changes in intestinal permeability [117]. It is possible that the same concept can be applied to the MTCT of HTLV-1. However, there is a lack of evidence recommending mixed nutrition immediately after birth.

4.2. Prevention Methods Other Than Nutritional Regimens

To prevent the MTCT of HIV, antiretroviral prophylaxis, cesarean section, and avoidance of breastfeeding are now sentinel events in resource-rich countries [118]. These are expected to be effective in preventing the MTCT of HTLV-1, which belongs to the same Retroviridae family.

Bittencourt et al. reported that when elective cesarean sections were performed in 81% of 41 HTLV-1 carrier pregnant women who opted for ExFF, no MTCT was observed in any of the 41 infants [119]. Although elective cesarean sections are expected to be effective in minimizing an infant's exposure to mother's blood containing infected cells, no high-quality studies have been conducted to date, and no evidence exists to support elective cesarean sections [15,71,84]. Conclusively, carrier pregnant women should not be generally indicated for cesarean section, as it may increase the risk of complications for mothers and children.

To date, no clinical trials have been conducted on ART during pregnancy, although in vitro studies have suggested efficacy of ART [71]. In a case series published in the United

Kingdom in 2021, zidovudine was administered to four mothers who developed ATL during pregnancy and to their babies. The authors reported that MTCT was observed in one of the four mothers, but the outcomes of the other three were unknown because of the short follow-up period [120]. Since there have been no studies on asymptomatic carriers who have not developed ATL, further investigation is warranted. Despite promising in vitro data, clinical data on the efficacy of antiretroviral drugs in preventing the MTCT of HTLV-1 are scarce [84].

Previous animal experimental and pilot studies have suggested that immunotherapy, such as neutralizing antibodies and vaccination with the HTLV-1 gene product, may protect against infection [121–124]. The ideal candidates and methods of inoculation remain to be elucidated. Furthermore, the correlates of the immune response have not yet been elucidated. Even if clinically effective vaccines and neutralizing antibodies are developed, they may be targeted first to those at high risk of sexual transmission, followed by the prevention of MTCT (see the review article by Ratner [125]).

5. Screening Program and Strategies for Prevention of MTCT in Japan

5.1. Background

Introduction of an HTLV-1 antibody screening program for all pregnant women remains controversial [88,91,126]. HTLV-1 antibody screening tests for all pregnant women are currently unavailable in countries except Japan. A nationwide antenatal HTLV-1 antibody screening program was implemented in Japan since 2010 owing to the following reasons: (i) HTLV-1 carriers are spread throughout Japan by internal population movement from endemic areas to non-endemic areas [127]; (ii) more than 4000 adolescents and adults are newly infected through sexual contact [58]; (iii) no effective drug treatment has been developed against this virus [128]; (iv) reduction in the number of these children would also contribute to a reduction in horizontal sources of transmission.

5.2. Screening Program in Practice

HTLV-1 antibody screening is usually performed within 30 weeks of gestation, allowing carriers sufficient time to obtain more information from their healthcare providers before delivery and select the appropriate feeding regimen for their infants. Pregnant women with positive screening results undergo confirmatory antibody testing using an algorithm (Figure 4) [54,129]. If a pregnant woman is determined to be a carrier, the healthcare provider will explain the risks of MTCT and preventive measures to the extent possible before delivery. If the mother does not have strong concerns about the risks of HTLV-1 associated diseases and interventions for MTCT, infant and child health examinations are performed on the same schedule (at 1, 3–4, 7–10, 18, and 36 months) as for infants born to non-carrier pregnant women. Testing for HTLV-1 antibodies at the age of three years to assess MTCT is recommended, but not mandatory [83].

5.3. Nutritional Regimens in Japan

Since 2017, the Japanese nutrition protocol for the prevention of postnatal MTCT via breast milk has changed from the three previous options of ExFF, STBF, and FTBMF to ExFF as the first choice with the most reliable preventive effect [83]. Based on the results of a recent cohort study and meta-analysis by Itabashi and Miyazawa [56,103], it was concluded that the MTCT rate for STBF would not exceed the risk of MTCT for ExFF unless the duration of breastfeeding does not exceed 90 days after birth and that adequate maternal support by a medical care provider is a precondition for ensuring this. Sufficient evidence to prove the effectiveness of FTBMF has not yet been obtained; therefore, it is not recommended [130]. Medical providers should not uniformly recommend ExFF to mothers from the perspective of MTCT prevention, but should fully explain the advantages and disadvantages of each nutritional regimen from the perspective of pregnancy, delivery, and childcare and provide shared decision-making support so that mothers can make their

own decisions about nutritional methods, including STBF and other nutritional regimens (Table 1) [54].

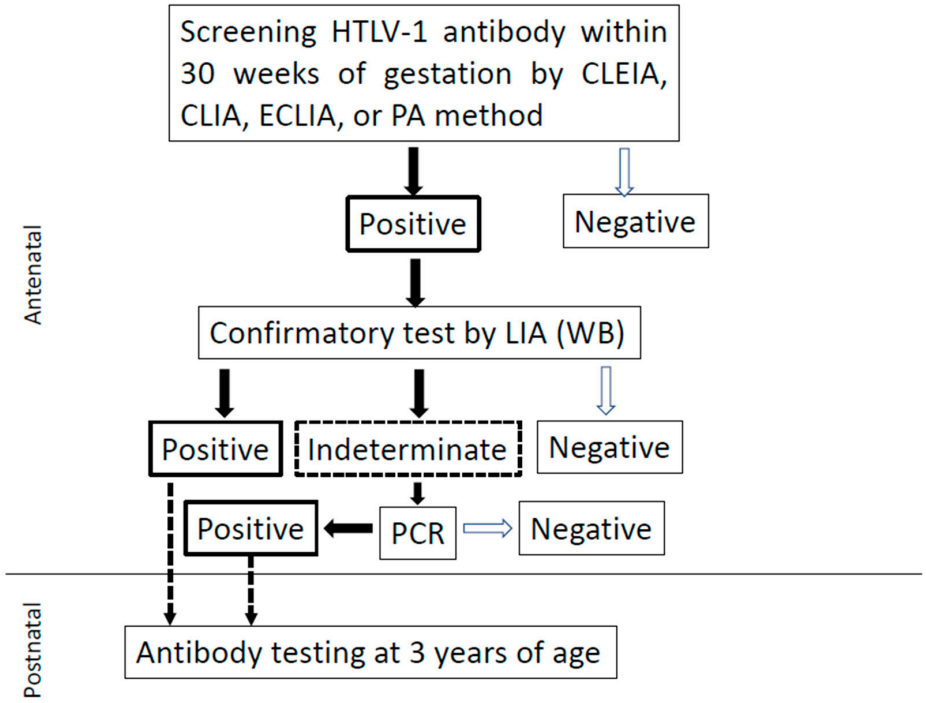

Figure 4. Algorithm for diagnosing HTLV-1 infection in Japan. Currently, no confirmatory tests using Western blotting are conducted in Japan. Flowchart for identifying HTLV-1 carriers among pregnant women. CLEIA, chemiluminescent enzyme immunoassay; CLIA, chemiluminescent immunoassay; ECLIA, electrochemiluminescent immunoassay; PA, particle agglutination; WB, Western blotting; LIA, line immunoassay; PCR, polymerase chain reaction. The figure is reproduced from Itabashi et al. [54]. For further details, please refer to Okuma et al. [129].

5.4. Issues of Nationwide Antenatal Screening Program in Japan

5.4.1. Support for Carrier Mothers

More than 10 years have passed since the screening test for all pregnant women was introduced in Japan. However, carrier mothers were not satisfied with the status quo. Their main opinions were as follows: (i) it is difficult to say that medical providers adequately support carrier mothers' choice of nutritional regimen, and (ii) there are no medical facilities close by where mothers can discuss their concerns about the onset of the disease or their children's infection, and they do not know whom to consult. This might be due to limited experience and insufficient knowledge of obstetricians and pediatricians about HTLV-1 infection, as well as lack of collaboration among obstetricians, pediatricians, hematologists or neurologists, and local government officials. Therefore, establishment of a consultation and support system for carrier mothers and their families based on local medical resources, along with public awareness of HTLV-1 infection, is an urgent issue.

5.4.2. Selection of Nutrition Regimen Considering Risk Factors

It is unclear whether it is appropriate to select ExFF or STBF without considering risk factors for MTCT. Deprivation of long-term breastfeeding in infants at very low risk for MTCT may impact their future health [131]. In addition, there are concerns about the impact of the selection of a nutrition regimen on mothers' parenting behavior and mother–infant bonding [132]. Future studies should accumulate data on infants born to

carrier mothers to determine the association between MTCT and its risk factors and to minimize the avoidance of breastfeeding.

5.4.3. Follow-Up of a Child Infected via MTCT

Although HAM/TSP is generally considered an adult manifestation of HTLV-1, the possibility of early-onset HAM/TSP via MTCT has long been reported, mainly in South America [133–135]. Yoshida et al. reported a case of childhood HAM/TSP in Japan in 1993 [136]; however, only a few cases have been reported since then.

Dermatological lesions, such as infectious dermatitis, atopic dermatitis, seborrheic dermatitis, acquired ichthyosis, candidiasis, palmar erythema, dermatophytosis, crusted scabies, and folliculitis decalvans, may be associated with HTLV-1 infection [137]. Cutaneous involvement in an apparently asymptomatic carrier has been considered a premonitory indication for the future development of either ATL or HAM/TSP [137]. As PVL may slightly fluctuate in asymptomatic children, measurement of PVL on a regular basis may not be of much clinical significance [138]. However, as early-onset HAM/TSP and ATL may be associated with a variety of skin lesions in addition to infectious dermatitis [133,134], serological tests and PVL measurements may be useful in children with known MTCT in endemic areas [138]. Children with known MTCT and suspected of having neurological abnormalities, such as weakness, muscle stiffness, spasm, gait disturbance, and abnormal urination, should be considered for PVL measurements. Skin lesions are also observed in such cases. The association between skin lesions and early-onset HAM/TSP in children in Japan has rarely been discussed. Since atopic dermatitis and seborrheic eczema occur frequently in infants in Japan, regardless of HTLV-1 infection, pediatricians are not concerned about their appearance in HTLV-1-infected children via MTCT. Longitudinal follow-up is needed to determine whether the relationship between skin lesions and premature HTLV-1-related disease in infected mother and child pairs in Japan differs from that in South America.

If MTCT is obvious, parents should consider at what age the child will be informed and who will inform the child of this fact. Furthermore, if the child is anxious, counseling may be necessary.

6. Conclusions

The perception of HTLV-1 infection as a "silent disease" has recently given way to concern that its presence may be having a variety of effects. Therefore, measures to prevent mother-to-child and horizontal transmissions are becoming increasingly important. Currently, no antiretroviral drugs or immunotherapies can be used clinically. More than 90% of MTCT cases involve trans-breastfeeding; therefore, the main preventive measures are avoidance of breastfeeding or reduction in infected cells in breast milk. Our study indicated that the MTCT rate of STBF within 90 days of birth in infants born to carrier mothers did not exceed that of ExFF. However, it is estimated that approximately 20% of mothers who choose STBF are unable to discontinue it by 90 days; therefore, adequate support from healthcare providers is essential. ExFF and STBF are available only in resource-rich areas with good sanitation. On the other hand, breastfeeding has various advantages. Accurate prediction based on risk factors for MTCT may curb more over-intervention cases for infants born to carrier mothers in resource-rich countries and reduce cases where the benefits of breastfeeding are traded off. However, in countries with limited medical resources, ExFF may not be a realistic option, particularly because it is directly associated with increased infant mortality. If antiretroviral drugs and immunotherapy, such as vaccines and neutralizing antibodies, are introduced in the future, it is expected that they may contribute to the prevention of MTCT after birth without compromising the advantages of breastfeeding and may even be useful for prenatal prevention of infection.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Showa University (No.1109, 7 October 2011).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher. The data presented in this study are available on request from the corresponding author.

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References

1. Moore, P.S.; Chang, Y. Why do viruses cause cancer? Highlights of the first century of human tumour virology. *Nat. Rev. Cancer* **2010**, *10*, 878–889. [CrossRef] [PubMed]
2. Gallo, R.C. Kyoto Workshop on some specific recent advances in human tumor virology. *Cancer Res.* **1981**, *41*, 4738–4739.
3. Hinuma, Y.; Nagata, K.; Hanaoka, M.; Nakai, M.; Matsumoto, T.; Kinoshita, K.; Shirakawa, S.; Miyoshi, I. Adult T-cell leukemia: Antigen in an ATL cell line and detection of antibodies to the antigen in human sera. *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 6476–6480. [CrossRef]
4. Gessain, A.; Vernant, J.; Maurs, L.; Barin, F.; Gout, O.; Calender, A.; De Thé, G. Antibodies to human t-lymphotropic virus type-i in patients with tropical spastic paraparesis. *Lancet* **1985**, *326*, 407–410. [CrossRef] [PubMed]
5. Osame, M.; Usuku, K.; Izumo, S.; Ijichi, N.; Amitani, H.; Igata, A.; Matsumoto, M.; Tara, M. HTLV-I associated myelopathy, a new clinical entity. *Lancet* **1986**, *1*, 1031–1032. [CrossRef]
6. Iwanaga, M.; Watanabe, T.; Yamaguchi, K. Adult T-cell leukemia: A review of epidemiological evidence. *Front. Microbiol.* **2012**, *3*, 322. [CrossRef] [PubMed]
7. Kaplan, J.E.; Osame, M.; Kubota, H.; Igata, A.; Nishitani, H.; Maeda, Y.; Khabbaz, R.F.; Janssen, R.S. The risk of development of HTLV-I-associated myelopathy/tropical spastic paraparesis among persons infected with HTLV-I. *J. Acquir. Immune Defic. Syndr.* **1990**, *3*, 1096–1101. [PubMed]
8. Maloney, E.M.; Cleghorn, F.R.; Morgan, O.S.C.; Rodgers-Johnson, P.; Cranston, B.; Jack, N.; Blattner, W.A.; Bartholomew, C.; Manns, A. Incidence of HTLV-I-Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP) in Jamaica and Trinidad. *J. Acquir. Immune Defic. Syndr. Hum. Retrovirology* **1998**, *17*, 167–170. [CrossRef]
9. Kamoi, K. HTLV-1 in Ophthalmology. *Front. Microbiol.* **2020**, *11*, 388. [CrossRef]
10. Schierhout, G.; McGregor, S.; Gessain, A.; Einsiedel, L.; Martinello, M.; Kaldor, J. Association between HTLV-1 infection and adverse health outcomes: A systematic review and meta-analysis of epidemiological studies. *Lancet Infect. Dis.* **2019**, *20*, 133–143. [CrossRef]
11. World Health Organization (WHO). Human T-lymphotropic Virus Type 1, Technical Report [Internet]. Available online: https://www.who.int/publications-detail-redirect/9789240020221 (accessed on 20 November 2022).
12. Cook, L.B.M.; Taylor, G.P. HTLV-1, The silent impact revealed. *Lancet Infect. Dis.* **2019**, *20*, 12–14. [CrossRef] [PubMed]
13. Gessain, A.; Cassar, O. Epidemiological Aspects and World Distribution of HTLV-1 Infection. *Front. Microbiol.* **2012**, *3*, 388. [CrossRef] [PubMed]
14. Eusebio-Ponce, E.; Anguita, E.; Paulino-Ramirez, R.; Candel, F.J. HTLV-1 infection: An emerging risk. Pathogenesis, epidemiology, diagnosis and associated diseases. *Rev. Esp. Quimioter.* **2019**, *32*, 485–496. [PubMed]
15. Carneiro-Proietti, A.B.F.; Amaranto-Damasio, M.S.; Leal-Horiguchi, C.F.; Bastos, R.H.C.; Seabra-Freitas, G.; Borowiak, D.R.; Ribeiro, M.A.; Proietti, F.A.; Ferreira, A.S.D.; Martins, M.L. Mother-to-child transmission of human T-Cell lymphotropic viruses-1/2, What we know, and what are the gaps in understanding and preventing this route of infection. *J. Pediatric. Infect Dis. Soc.* **2014**, *3* (Suppl. 1), S24–S29. [CrossRef] [PubMed]
16. Bartholomew, C.; Jack, N.; Edwards, J.; Charles, W.; Corbin, D.; Cleghorn, F.R.; Blattner, W.A. HTLV-I serostatus of mothers of patients with adult T-cell leukemia and HTLV-I-associated myelopathy/tropical spastic paraparesis. *J. Hum. Virol.* **1999**, *1*, 302–305.

17. Bangham, C.R.M.; Miura, M.; Kulkarni, A.; Matsuoka, M. Regulation of Latency in the Human T Cell Leukemia Virus, HTLV-1. *Annu. Rev. Virol.* **2019**, *6*, 365–385. [CrossRef]
18. Demontis, M.A.; Sadiq, M.T.; Golz, S.; Taylor, G.P. HTLV-1 viral RNA is detected rarely in plasma of HTLV-1 infected subjects. *J. Med. Virol.* **2015**, *87*, 2130–2134. [CrossRef]
19. Sato, H.; Orensteint, J.; Dimitrov, D.; Martin, M. Cell-to-cell spread of HIV-1 occurs within minutes and may not involve the participation of virus particles. *Virology* **1992**, *186*, 712–724. [CrossRef]
20. Jolly, C. Cell-to-cell transmission of retroviruses: Innate immunity and interferon-induced restriction factors. *Virology* **2011**, *411*, 251–259. [CrossRef]
21. Nejmeddine, M.; Bangham, C.R. The HTLV-1 Virological Synapse. *Viruses* **2010**, *2*, 1427–1447. [CrossRef]
22. Van Prooyen, N.; Gold, H.; Andresen, V.; Schwartz, O.; Jones, K.; Ruscetti, F.; Lockett, S.; Gudla, P.; Venzon, D.; Franchini, G. Human T-cell leukemia virus type 1 p8 protein increases cellular conduits and virus transmission. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20738–20743. [CrossRef]
23. Pais-Correia, A.M.; Sachse, M.; Guadagnini, S.; Robbiati, V.; Lasserre, R.; Gessain, A.; Gout, O.; Alcover, A.; Thoulouze, M.I. Biofilm-like extracellular viral assemblies mediate HTLV-1 cell-to-cell transmission at virological synapses. *Nat. Med.* **2010**, *16*, 83–89. [CrossRef] [PubMed]
24. Pinto, D.O.; Al Sharif, S.; Mensah, G.; Cowen, M.; Khatkar, P.; Erickson, J.; Branscome, H.; Lattanze, T.; DeMarino, C.; Alem, E.; et al. Extracellular vesicles from HTLV-1 infected cells modulate target cells and viral spread. *Retrovirology* **2021**, *18*, 6. [CrossRef] [PubMed]
25. Hiyoshi, M.; Takahashi, N.; Eltalkhawy, Y.M.; Noyori, O.; Lotfi, S.; Panaampon, J.; Okada, S.; Tanaka, Y.; Ueno, T.; Fujisawa, J.; et al. M-Sec induced by HTLV-1 mediates an efficient viral transmission. Swanstrom R, editor. *PLOS Pathog.* **2021**, *17*, e1010126. [CrossRef]
26. Hirons, A.; Khoury, G.; Purcell, D.F.J. Human T-cell lymphotropic virus type-1, A lifelong persistent infection, yet never truly silent. *Lancet Infect. Dis.* **2020**, *21*, e2–e10. [CrossRef] [PubMed]
27. Pique, C.; Jones, K.S. Pathways of cell-cell transmission of HTLV-1. *Front. Microbiol.* **2012**, *3*, 378. [CrossRef] [PubMed]
28. Manel, N.; Kim, F.J.; Kinet, S.; Taylor, N.; Sitbon, M.; Battini, J.L. The ubiquitous glucose transporter GLUT-1 is a receptor for HTLV. *Cell* **2003**, *115*, 449–459. [CrossRef]
29. Ghez, D.; Lepelletier, Y.; Lambert, S.; Fourneau, J.M.; Blot, V.; Janvier, S.; Arnulf, B.; van Endert, P.M.; Heveker, N.; Pique, C.; et al. Neuropilin-1 Is Involved in Human T-Cell Lymphotropic Virus Type 1 Entry. *J. Virol.* **2006**, *80*, 6844–6854. [CrossRef]
30. Jones, K.S.; Petrow-Sadowski, C.; Bertolette, D.C.; Huang, Y.; Ruscetti, F.W. Heparan sulfate proteoglycans mediate attachment and entry of human T-cell leukemia virus type 1 virions into CD4+ T cells. *J. Virol.* **2005**, *79*, 12692–12702. [CrossRef]
31. Lambert, S.; Bouttier, M.; Vassy, R.; Seigneuret, M.; Petrow-Sadowski, C.; Janvier, S.; Heveker, N.; Ruscetti, F.W.; Perret, G.; Jones, K.S.; et al. HTLV-1 uses HSPG and neuropilin-1 for entry by molecular mimicry of VEGF165. *Blood* **2009**, *113*, 5176–5185. [CrossRef]
32. Jones, K.S.; Petrow-Sadowski, C.; Huang, Y.K.; Bertolette, D.C.; Ruscetti, F.W. Cell-free HTLV-1 infects dendritic cells leading to transmission and transformation of CD4(+) T cells. *Nat. Med.* **2008**, *14*, 429–436. [CrossRef] [PubMed]
33. Jain, P.; Manuel, S.L.; Khan, Z.K.; Ahuja, J.; Quann, K.; Wigdahl, B. DC-SIGN mediates cell-free infection and transmission of human T-cell lymphotropic virus type 1 by dendritic cells. *J. Virol.* **2009**, *83*, 10908–10921. [CrossRef] [PubMed]
34. Assil, S.; Futsch, N.; Décembre, E.; Alais, S.; Gessain, A.; Cosset, F.L.; Mahieux, R.; Dreux, M.; Hélène Dutartre, H. Sensing of cell-associated HTLV by plasmacytoid dendritic cells is regulated by dense β-galactoside glycosylation. *PLoS Pathog.* **2019**, *15*, e1007589. [CrossRef]
35. Koyanagi, Y.; Itoyama, Y.; Nakamura, N.; Takamatsu, K.; Kira, J.; Iwamasa, T.; Goto, I.; Yamamoto, N. In vivo infection of human T-cell leukemia virus type I in non-T cells. *Virology* **1993**, *196*, 25–33. [CrossRef]
36. Richardson, J.H.; Edwards, A.J.; Cruickshank, J.K.; Rudge, P.; Dalgleish, A.G. In vivo cellular tropism of human T-cell leukemia virus type 1. *J. Virol.* **1990**, *64*, 5682–5687. [CrossRef] [PubMed]
37. Nagai, M.; Brennan, M.B.; Sakai, J.A.; Mora, C.A.; Jacobson, S. CD8(+) T cells are an in vivo reservoir for human T-cell lymphotropic virus type I. *Blood* **2001**, *98*, 1858–1861. [CrossRef]
38. Macatonia, S.E.; Cruickshank, J.K.; Rudge, P.; Knight, S.C. Dendritic cells from patients with tropical spastic paraparesis are infected with HTLV-1 and stimulate autologous lymphocyte proliferation. *AIDS Res. Hum. Retroviruses* **1992**, *8*, 1699–1706. [CrossRef]
39. Hishizawa, M.; Imada, K.; Kitawaki, T.; Ueda, M.; Kadowaki, N.; Uchiyama, T. Depletion and impaired interferon-alpha-producing capacity of blood plasmacytoid dendritic cells in human T-cell leukaemia virus type I-infected individuals. *Br. J. Haematol.* **2004**, *125*, 568–575. [CrossRef]
40. de Castro-Amarante, M.F.; Pise-Masison, C.A.; McKinnon, K.; Washington Parks, R.; Galli, V.; Omsland, M.; Andresen, V.; Massoud, R.; Brunetto, G.; Caruso, B.; et al. Human T Cell Leukemia Virus Type 1 Infection of the Three Monocyte Subsets Contributes to Viral Burden in Humans. *J. Virol.* **2015**, *90*, 2195–2207. [CrossRef]
41. Igakura, T.; Stinchcombe, J.C.; Goon, P.K.C.; Taylor, G.P.; Weber, J.N.; Griffiths, G.M.; Tanaka, Y.; Osame, M.; Bangham, C.R.M. Spread of HTLV-I between lymphocytes by virus-induced polarization of the cytoskeleton. *Science* **2003**, *299*, 1713–1716. [CrossRef]

42. Melamed, A.; Laydon, D.J.; Gillet, N.A.; Tanaka, Y.; Taylor, G.P.; Bangham, C.R.M. Genome-wide determinants of proviral targeting, clonal abundance and expression in natural HTLV-1 infection. *PLoS Pathog.* **2013**, *9*, e1003271. [CrossRef]
43. Miura, M.; Naito, T.; Saito, M. Current Perspectives in Human T-Cell Leukemia Virus Type 1 Infection and Its Associated Diseases. *Front. Med.* **2022**, *9*, 867478. [CrossRef] [PubMed]
44. Martin, J.L.; Maldonado, J.O.; Mueller, J.D.; Zhang, W.; Mansky, L.M. Molecular Studies of HTLV-1 Replication: An Update. *Viruses* **2016**, *8*, 31. [CrossRef] [PubMed]
45. Gillet, N.A.; Malani, N.; Melamed, A.; Gormley, N.; Carter, R.; Bentley, D.; Berry, C.; Bushman, F.D.; Taylor, G.P.; Bangham, C.R.M. The host genomic environment of the provirus determines the abundance of HTLV-1-infected T-cell clones. *Blood* **2011**, *117*, 3113–3122. [CrossRef]
46. Carpentier, A.; Barez, P.Y.; Hamaidia, M.; Gazon, H.; de Brogniez, A.; Perike, S.; Gillet, N.; Willems, L. Modes of Human T Cell Leukemia Virus Type 1 Transmission, Replication and Persistence. *Viruses* **2015**, *7*, 3603–3624. [CrossRef] [PubMed]
47. Kannagi, M.; Harada, S.; Maruyama, I.; Inoko, H.; Igarashi, H.; Kuwashima, G.; Sato, S.; Morita, M.; Kidokoro, M.; Sugimoto, M.; et al. Predominant recognition of human T cell leukemia virus type I (HTLV-I) pX gene products by human CD8+ cytotoxic T cells directed against HTLV-I-infected cells. *Int. Immunol.* **1991**, *3*, 761–767. [CrossRef]
48. Tanaka, A.; Matsuoka, M. HTLV-1 Alters T Cells for Viral Persistence and Transmission. *Front. Microbiol.* **2018**, *9*, 461. [CrossRef]
49. Ma, G.; Yasunaga, J.I.; Matsuoka, M. Multifaceted functions and roles of HBZ in HTLV-1 pathogenesis. *Retrovirology* **2016**, *13*, 16. [CrossRef]
50. Kashanchi, F.; Brady, J.N. Transcriptional and post-transcriptional gene regulation of HTLV-1. *Oncogene* **2005**, *24*, 5938–5951. [CrossRef]
51. Edwards, D.; Fenizia, C.; Gold, H.; de Castro-Amarante, M.F.; Buchmann, C.; Pise-Masison, C.A.; Franchini, G. Orf-I and orf-II-encoded proteins in HTLV-1 infection and persistence. *Viruses* **2011**, *3*, 861–885. [CrossRef]
52. Moles, R.; Sarkis, S.; Galli, V.; Omsland, M.; Purcell, D.F.J.; Yurick, D.; Khoury, G.; Pise-Masison, C.A.; Franchini, G. p30 protein: A critical regulator of HTLV-1 viral latency and host immunity. *Retrovirology* **2019**, *16*, 42. [CrossRef] [PubMed]
53. Omsland, M.; Silic-Benussi, M.; Moles, R.; Sarkis, S.; Purcell, D.F.J.; Yurick, D.; Khoury, G.; D'Agostino, D.M.; Ciminale, V.; Franchini, G. Functional properties and sequence variation of HTLV-1 p13. *Retrovirology* **2020**, *17*, 11. [CrossRef]
54. Itabashi, K.; Miyazawa, T. Mother-to-Child Transmission of Human T-Cell Leukemia Virus Type 1, Mechanisms and Nutritional Strategies for Prevention. *Cancers* **2021**, *13*, 4100. [CrossRef] [PubMed]
55. Suzuki, S.; Tanaka, M.; Matsuda, H.; Tsukahara, Y.; Kuribayashi, Y.; Nakai, A.; Miyazaki, R.; Kamiya, N.; Sekizawa, A.; Mizutani, N.; et al. Prevalence of human T-cell leukemia virus type 1 carrier in Japanese pregnant women in 2013. *J. Clin. Med. Res.* **2015**, *7*, 499–500. [CrossRef]
56. Itabashi, K.; Miyazawa, T.; Nerome, Y.; Sekizawa, A.; Moriuchi, H.; Saito, S.; Yonemoto, N. Issues of infant feeding for postnatal prevention of human T-cell leukemia/lymphoma virus type-1 mother-to-child transmission. *Pediatr. Int.* **2021**, *63*, 284–289. [CrossRef] [PubMed]
57. Okochi, K.; Sato, H. Transmission of ATLV (HTLV-I) through blood transfusion. *Int. Symp. Princess Takamatsu Cancer Res. Fund.* **1984**, *15*, 129–135.
58. Satake, M.; Iwanaga, M.; Sagara, Y.; Watanabe, T.; Okuma, K.; Hamaguchi, I. Incidence of human T-lymphotropic virus 1 infection in adolescent and adult blood donors in Japan: A nationwide retrospective cohort analysis. *Lancet Infect. Dis.* **2016**, *16*, 1246–1254. [CrossRef]
59. Gallo, R.C.; Willems, L.; Hasegawa, H. Global Virus Network's Task Force on HTLV-1. Screening transplant donors for HTLV-1 and -2. *Blood* **2016**, *128*, 3029–3031. [CrossRef]
60. Stuver, S.O.; Tachibana, N.; Okayama, A.; Shioiri, S.; Tsunetoshi, Y.; Tsuda, K.; Mueller, N.E. Heterosexual transmission of human T cell leukemia/lymphoma virus type I among married couples in southwestern Japan: An initial report from the Miyazaki Cohort Study. *J. Infect. Dis.* **1993**, *167*, 57–65. [CrossRef]
61. Paiva, A.; Casseb, J. Sexual transmission of human T-cell lymphotropic virus type 1. *Rev. Soc. Bras. Med. Trop.* **2014**, *47*, 265–274. [CrossRef]
62. Silva, M.T.T.; Harab, R.C.; Leite, A.C.; Schor, D.; Araújo, A.; Andrada-Serpa, M.J. Human T lymphotropic virus type 1 (HTLV-1) proviral load in asymptomatic carriers, HTLV-1-associated myelopathy/tropical spastic paraparesis, and other neurological abnormalities associated with HTLV-1 infection. *Clin. Infect. Dis.* **2007**, *44*, 689–692. [CrossRef] [PubMed]
63. Iwanaga, M.; Watanabe, T.; Utsunomiya, A.; Okayama, A.; Uchimaru, K.; Koh, K.R.; Ogata, M.; Kikuchi, H.; Sagara, Y.; Uozumi, K.; et al. Human T-cell leukemia virus type I (HTLV-1) proviral load and disease progression in asymptomatic HTLV-1 carriers: A nationwide prospective study in Japan. *Blood* **2010**, *116*, 1211–1219. [CrossRef]
64. Primo, J.; Siqueira, I.; Nascimento, M.C.F.; Oliveira, M.F.; Farre, L.; Carvalho, E.M.; Bittencourt, A.L. High HTLV-1 proviral load, a marker for HTLV-1 associated myelopathy/tropical spastic paraparesis, is also detected in patients with infective dermatitis associated with HTLV-1. *Braz. J. Med. Biol. Res.* **2009**, *42*, 761–764. [CrossRef]

65. Sugimoto, M.; Mita, S.; Tokunaga, M.; Yamaguchi, K.; Cho, I.; Matsumoto, M.; Mochizuki, M.; Araki, S.; Takatsuki, K.; M Ando, M. Pulmonary involvement in human T-cell lymphotropic virus type-I uveitis: T-lymphocytosis and high proviral DNA load in bronchoalveolar lavage fluid. *Eur. Respir. J.* **1993**, *6*, 938–943. [CrossRef]
66. Gabet, A.S.; Mortreux, F.; Talarmin, A.; Plumelle, Y.; Leclercq, I.; Leroy, A.; Gessain, A.; Clity, E.; Joubert, M.; Wattel, E. High circulating proviral load with oligoclonal expansion of HTLV-1 bearing T cells in HTLV-1 carriers with strongyloidiasis. *Oncogene* **2000**, *19*, 4954–4960. [CrossRef] [PubMed]
67. Murphy, E.L. Sexual Transmission of Human T-Lymphotropic Virus Type I (HTLV-I). *Ann. Intern. Med.* **1989**, *111*, 555. [CrossRef] [PubMed]
68. Hino, S. Establishment of the milk-borne transmission as a key factor for the peculiar endemicity of human T-lymphotropic virus type 1 (HTLV-1): The ATL Prevention Program Nagasaki. *Proc. Jpn. Acad. Ser. B Phys. Biol. Sci.* **2011**, *87*, 152–166. [CrossRef] [PubMed]
69. Wiktor, S.Z.; Pate, E.J.; Rosenberg, P.S.; Barnett, M.; Palmer, P.; Medeiros, D.; Maloney, E.M.; Blattner, W.A. Mother-to-child transmission of human T-cell lymphotropic virus type I associated with prolonged breast-feeding. *J. Hum. Virol.* **1997**, *1*, 37–44.
70. Moriuchi, H.; Masuzaki, H.; Doi, H.; Katamine, S. Mother-to-child transmission of human T-cell lymphotropic virus type 1. *Pediatr. Infect. Dis. J.* **2013**, *32*, 175–177. [CrossRef]
71. Rosadas, C.; Taylor, G.P. Mother-to-Child HTLV-1 Transmission: Unmet Research Needs. *Front. Microbiol.* **2019**, *10*, 999. [CrossRef]
72. Tezuka, K.; Fuchi, N.; Okuma, K.; Tsukiyama, T.; Miura, S.; Hasegawa, Y.; Sasaki, D.; Sasaki, E.; Mizukami, T.; Kuramitsu, M.; et al. HTLV-1 targets human placental trophoblasts in seropositive pregnant women. *J. Clin. Invest.* **2020**, *130*, 6171–6186. [CrossRef] [PubMed]
73. Martin-Latil, S.; Gnadig, N.F.; Mallet, A.; Desdouits, M.; Guivel-Benhassine, F.; Jeannin, P.; Prevost, M.; Schwartz, O.; Gessain, A.; Ozden, S.; et al. Transcytosis of HTLV-1 across a tight human epithelial barrier and infection of subepithelial dendritic cells. *Blood* **2012**, *120*, 572–580. [CrossRef]
74. Kinoshita, K.; Yamanouchi, K.; Ikeda, S.; Momita, S.; Amagasaki, T.; Soda, H.; Ichimaru, M.; Moriuchi, R.; Katamine, S.; Miyamoto, T.; et al. Oral Infection of a Common Marmoset with Human T-Cell Leukemia Virus Type-I (htlv-I) by Inoculating Fresh Human Milk of Htlv-I Carrier Mothers. *Jpn. J. Cancer Res. GANN* **1985**, *76*, 1147–1153. [PubMed]
75. Kashiwagi, K.; Furusyo, N.; Nakashima, H.; Kubo, N.; Kinukawa, N.; Kashiwagi, S.; Hayashi, J. A decrease in mother-to-child transmission of human t lymphotropic virus type i (htlv-i) in okinawa, Japan. *Am. J. Trop. Med. Hyg.* **2004**, *70*, 158–163. [CrossRef] [PubMed]
76. Witkowska-Zimny, M.; Kaminska-El-Hassan, E. Cells of Human Breast Milk. *Cell. Mol. Biol. Lett.* **2017**, *22*, 11. Available online: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5508878/ (accessed on 26 March 2023). [CrossRef]
77. Southern, S.O.; Southern, P.J. Persistent HTLV-I infection of breast luminal epithelial cells: A role in HTLV transmission? *Virology* **1998**, *241*, 200–214. [CrossRef]
78. LeVasseur, R.J.; Southern, S.O.; Southern, P.J. Mammary epithelial cells support and transfer productive human T-cell lymphotropic virus infections. *J. Hum. Virol.* **1998**, *1*, 214–223.
79. Takeuchi, H.; Takahashi, M.; Norose, Y.; Takeshita, T.; Fukunaga, Y.; Takahashi, H. Transformation of breast milk macrophages by HTLV-I: Implications for HTLV-I transmission via breastfeeding. *Biomed. Res.* **2010**, *31*, 53–61. [CrossRef]
80. Percher, F.; Jeannin, P.; Martin-Latil, S.; Gessain, A.; Afonso, P.V.; Vidy-Roche, A.; Ceccaldi, P.E. Mother-to-Child Transmission of HTLV-1 Epidemiological Aspects, Mechanisms and Determinants of Mother-to-Child Transmission. *Viruses* **2016**, *8*, 40. [CrossRef]
81. Ohata, J.; Matsuoka, M.; Yamashita, T.; Tojo, A.; Tani, K.; Asano, S. CD4/CD8 double-positive adult T cell leukemia with preceding cytomegaloviral gastroenterocolitis. *Int. J. Hematol.* **1999**, *69*, 92–95.
82. Tugizov, S.M.; Herrera, R.; Veluppillai, P.; Greenspan, D.; Soros, V.; Greene, W.C.; Ceccaldi, P.E. Differential transmission of HIV traversing fetal oral/intestinal epithelia and adult oral epithelia. *J. Virol.* **2012**, *86*, 2556–2570. [CrossRef]
83. Itabashi, K.; Miyazawa, T.; Sekizawa, A.; Tokita, A.; Saito, S.; Moriuchi, H.; Nerome, Y.; Uchimaru, K.; Watanabe, T. A Nationwide Antenatal Human T-Cell Leukemia Virus Type-1 Antibody Screening in Japan. *Front. Microbiol.* **2020**, *11*, 595. [CrossRef]
84. Rosadas, C.; Taylor, G.P. Current Interventions to Prevent HTLV-1 Mother-to-Child Transmission and Their Effectiveness: A Systematic Review and Meta-Analysis. *Microorganisms* **2022**, *10*, 2227. [CrossRef]
85. Plancoulaine, S.; Buigues, R.P.; Murphy, E.L.; van Beveren, M.; Pouliquen, J.F.; Joubert, M.; Rémy, F.; Tuppin, P.; Tortevoye, P.; de Thé, G.; et al. Demographic and familial characteristics of HTLV-1 infection among an isolated, highly endemic population of African origin in French Guiana. *Int. J. Cancer* **1998**, *76*, 331–336. [CrossRef]
86. Plancoulaine, S.; Gessain, A.; Joubert, M.; Tortevoye, P.; Jeanne, I.; Talarmin, A.; de Thé, G.; Abel, L. Detection of a major gene predisposing to human T lymphotropic virus type I infection in children among an endemic population of African origin. *J. Infect. Dis.* **2000**, *182*, 405–412. [CrossRef] [PubMed]
87. Filippone, C.; Bassot, S.; Betsem, E.; Tortevoye, P.; Guillotte, M.; Mercereau-Puijalon, O.; Plancoulaine, S.; Calattini, S.; Gessain, A. A New and Frequent Human T-Cell Leukemia Virus Indeterminate Western Blot Pattern: Epidemiological Determinants and PCR Results in Central African Inhabitants. *J. Clin. Microbiol.* **2012**, *50*, 1663–1672. [CrossRef]
88. Rosadas, C.; Malik, B.; Taylor, G.P.; Puccioni-Sohler, M. Estimation of HTLV-1 vertical transmission cases in Brazil per annum. *PLoS Negl. Trop. Dis.* **2018**, *12*, e0006913. [CrossRef] [PubMed]

89. Rosadas, C.; Woo, T.; Haddow, J.; Rowan, A.; Taylor, G.P. Anti-HTLV-1/2 IgG Antibodies in the Breastmilk of Seropositive Mothers. *Microorganisms* **2021**, *9*, 1413. [CrossRef] [PubMed]
90. Fuchi, N.; Miura, K.; Tsukiyama, T.; Sasaki, D.; Ishihara, K.; Tsuruda, K.; Hasegawa, H.; Miura, S.; Yanagihara, K.; Masuzaki, H. Natural Course of Human T-Cell Leukemia Virus Type 1 Proviral DNA Levels in Carriers During Pregnancy. *J. Infect. Dis.* **2018**, *217*, 1383–1389. [CrossRef]
91. Paiva, A.M.; Assone, T.; Haziot, M.E.J.; Smid, J.; Fonseca, L.A.M.; Luiz, O.D.C.; de Oliveira, J.A.C.P.; Casseb, J. Risk factors associated with HTLV-1 vertical transmission in Brazil: Longer breastfeeding, higher maternal proviral load and previous HTLV-1-infected offspring. *Sci. Rep.* **2018**, *8*, 7742. [CrossRef] [PubMed]
92. Albenzio, M.; Santillo, A.; Stolfi, I.; Manzoni, P.; Iliceto, A.; Rinaldi, M.; Magaldi, R. Lactoferrin Levels in Human Milk after Preterm and Term Delivery. *Amer J. Perinatol.* **2016**, *33*, 1085–1089. [CrossRef] [PubMed]
93. Ureta-Vidal, A.; Angelin-Duclos, C.; Tortevoye, P.; Murphy, E.; Lepère, J.F.; Buigues, R.P.; Jolly, N.; Joubert, M.; Carles, G.; Pouliquen, J.F.; et al. Mother-to-child transmission of human T-cell-leukemia/lymphoma virus type I: Implication of high antiviral antibody titer and high proviral load in carrier mothers. *Int. J. Cancer* **1999**, *82*, 832–836. [CrossRef]
94. Gotuzzo, E.; Moody, J.; Verdonck, K.; Cabada, M.M.; González, E.; Van Dooren, S.; Vandamme, A.M.; Terashima, A.; Vermund, S.H. Frequent HTLV-1 infection in the offspring of Peruvian women with HTLV-1-associated myelopathy/tropical spastic paraparesis or strongyloidiasis. *Rev. Panam. Salud. Publica.* **2007**, *22*, 223–230. [CrossRef]
95. Yoshinaga, M.; Yashiki, S.; Oki, T.; Fujiyoshi, T.; Nagata, Y.; Sonoda, S. A maternal risk factor for mother-to-child HTLV-I transmission: Viral antigen-producing capacities in culture of peripheral blood and breast milk cells. *Jpn. J. Cancer Res.* **1995**, *86*, 649–654. [CrossRef] [PubMed]
96. Biggar, R.J.; Ng, J.; Kim, N.; Hisada, M.; Li, H.C.; Cranston, B.; Hanchard, B.; Maloney, E.M. Human leukocyte antigen concordance and the transmission risk via breast-feeding of human T cell lymphotropic virus type I. *J. Infect. Dis.* **2006**, *193*, 277–282. [CrossRef]
97. Morita, Y.; Campos-Alberto, E.; Yamaide, F.; Nakano, T.; Ohnisi, H.; Kawamoto, M.; Kawamoto, N.; Matsui, E.; Kondo, N.; Kohno, Y.; et al. TGF-β Concentration in Breast Milk is Associated with the Development of Eczema in Infants. *Front. Pediatr.* **2018**, *6*, 162. Available online: https://www.frontiersin.org/articles/10.3389/fped.2018.00162/full (accessed on 26 March 2023). [CrossRef]
98. Moriuchi, M.; Moriuchi, H. Transforming growth factor-β enhances human T-cell leukemia virus type I infection. *J. Med. Virol.* **2002**, *67*, 427–430. [CrossRef]
99. Moriuchi, M.; Moriuchi, H. A Milk Protein Lactoferrin Enhances Human T Cell Leukemia Virus Type I and Suppresses HIV-1 Infection. *J. Immunol.* **2001**, *166*, 4231–4236. [CrossRef]
100. Moriuchi, M.; Moriuchi, H. Induction of lactoferrin gene expression in myeloid or mammary gland cells by human T-cell leukemia virus type 1 (HTLV-1) tax: Implications for milk-borne transmission of HTLV-1. *J. Virol.* **2006**, *80*, 7118–7126. [CrossRef]
101. Nerome, Y.; Kojyo, K.; Ninomiya, Y.; Ishikawa, T.; Ogiso, A.; Takei, S.; Kawano, Y.; Douchi, T.; Takezaki, T.; Owaki, T. Current human T-cell lymphotropic virus type 1 mother-to-child transmission prevention status in Kagoshima. *Pediatr. Int.* **2014**, *56*, 640–643. [CrossRef]
102. New WHO Report on Human T-Lymphotropic Virus Type 1 Highlights Strategies for Its Prevention and Control [Internet]. Available online: https://www.who.int/news/item/03-03-2021-new-who-report-on-human-t-lymphotropic-virus-type-1-indicates-the-future-path-for-its-prevention-and-control (accessed on 26 March 2023).
103. Miyazawa, T.; Hasebe, Y.; Murase, M.; Sakurai, M.; Itabashi, K.; Yonemoto, N. The Effect of Early Postnatal Nutrition on Human T Cell Leukemia Virus Type 1 Mother-to-Child Transmission: A Systematic Review and Meta-Analysis. *Viruses* **2021**, *13*, 819. [CrossRef] [PubMed]
104. Carroll, C.; Booth, A.; Campbell, F.; Relton, C. Qualitative evidence synthesis of values and preferences to inform infant feeding in the context of non-HIV transmission risk. *PLoS ONE* **2020**, *15*, e0242669. [CrossRef] [PubMed]
105. Millen, S.; Thoma-Kress, A.K. Milk Transmission of HTLV-1 and the Need for Innovative Prevention Strategies. *Front. Med.* **2022**, *9*, 867147. [CrossRef]
106. Masuzaki, H.; Moriuchi, H.; Miura, K.; Uehira, S. 25 Nenkan Keizoku Shita Ninpu no HTLV-I Kōtai Kensa Kekka Kara Erareta Boshikansen Yobō Kōka No Kenshō Oyobi Kōseido Sukurīningu Shisutemu Kaihatsu. Health Labour Sciences Research Grant [Internet]. 2013. Available online: https://mhlw-grants.niph.go.jp/niph/search/NIDD00.do?resrchNum=201318019B (accessed on 16 November 2019).
107. Takezaki, T. Kagoshima-ken ni okeru HTLV-I kyaria haha karano shuseiji ni okeru tuiseki kenkyū. *Health Labour Sci. Res. Grant.* **2009**, 59–61. Available online: https://www.mhlw.go.jp/bunya/kodomo/boshi-hoken16/dl/02_4.pdf (accessed on 30 January 2021). (In Japanese).
108. Ekuni, Y. Prevention of HTLV-1 vertical infection: Usefulness of frozen-thawed breast milk. *Adv. Obstet. Gynecol.* **1997**, *49*, 171–179.
109. Ando, Y.; Ekuni, Y.; Matsumoto, Y.; Nakano, S.; Saito, K.; Kakimoto, K.; Tanigawa, T.; Kawa, M.; Toyama, T. Long-term serological outcome of infants who received frozen-thawed milk from human T-lymphotropic virus type-I positive mothers. *J. Obstet. Gynaecol. Res.* **2004**, *30*, 436–438. [CrossRef] [PubMed]
110. Miller, J.; Tonkin, E.; Damarell, R.A.; McPhee, A.J.; Suganuma, M.; Suganuma, H.; Middleton, P.F.; Makrides, M.; Collins, C.T. A Systematic Review and Meta-Analysis of Human Milk Feeding and Morbidity in Very Low Birth Weight Infants. *Nutrients* **2018**, *10*, 707. [CrossRef]

111. Arslanoglu, S.; Bertino, E.; Tonetto, P.; De Nisi, G.; Ambruzzi, A.M.; Biasini, A.; Profeti, C.; Spreghini, M.R.; Moro, G.E.; Italian Association of Human Milk Banks Associazione Italiana Banche del Latte Umano Donato (AIBLUD: www.aiblud.org). Guidelines for the establishment and operation of a donor human milk bank. *J. Matern. Fetal. Neonatal. Med.* **2010**, *23* (Suppl. 2), 1–20. [CrossRef]
112. Pitino, M.A.; O'Connor, D.L.; McGeer, A.J.; Unger, S. The impact of thermal pasteurization on viral load and detectable live viruses in human milk and other matrices: A rapid review. *Appl. Physiol. Nutr. Metab.* **2021**, *46*, 10–26. [CrossRef]
113. Yamato, K.; Taguchi, H.; Yoshimoto, S.; Fujishita, M.; Yamashita, M.; Ohtsuki, Y.; Hoshino, H.; Miyoshi, I. Inactivation of lymphocyte-transforming activity of human T-cell leukemia virus type I by heat. *Jpn. J. Cancer Res.* **1986**, *77*, 13–15.
114. Rigourd, V.; Meyer, V.; Kieffer, F.; Aubry, S.; Magny, J.F. HTLV and "donating" milk. *Bull Soc. Pathol. Exot.* **2011**, *104*, 205–208. [CrossRef]
115. O'Connor, D.L.; Ewaschuk, J.B.; Unger, S. Human milk pasteurization: Benefits and risks. *Curr. Opin. Clin. Nutr. Metab. Care* **2015**, *18*, 269–275. [CrossRef] [PubMed]
116. Njom Nlend, A.E.; Motaze, A.C.N.; Sandie, A.; Fokam, J. HIV-1 transmission and survival according to feeding options in infants born to HIV-infected women in Yaoundé, Cameroon. *BMC Pediatr.* **2018**, *18*, 69. [CrossRef] [PubMed]
117. O'Sullivan, A.; Farver, M.; Smilowitz, J.T. The Influence of Early Infant-Feeding Practices on the Intestinal Microbiome and Body Composition in Infants. *Nutr. Metab. Insights* **2015**, *8* (Suppl. 1), 1–9.
118. Mepham, S.O.; Bland, R.M.; Newell, M.L. Prevention of mother-to-child transmission of HIV in resource-rich and -poor settings. *BJOG* **2011**, *118*, 202–218. [CrossRef]
119. Bittencourt, A.L.; Sabino, E.C.; Costa, M.C.; Pedroso, C.; Moreira, L. No evidence of vertical transmission of HTLV-I in bottle-fed children. *Rev. Do Inst. Med. Trop. São Paulo* **2002**, *44*, 63–65. [CrossRef] [PubMed]
120. Motedayen Aval, L.; Boullier, M.; Lyall, H.; Collins, G.P.; Ayto, R.; Kelly, D.F.; Tedder, R.S.; Drysdale, S.B.; Taylor, G.P.; Cook, L.B. Adult T cell leukaemia/lymphoma (ATL) in pregnancy: A UK case series. *eJHaem* **2021**, *2*, 134–138. [CrossRef] [PubMed]
121. Sawada, T.; Iwahara, Y.; Ishii, K.; Taguchi, H.; Hoshino, H.; Miyoshi, I. Immunoglobulin prophylaxis against milkborne transmission of human T cell leukemia virus type I in rabbits. *J. Infect. Dis.* **1991**, *164*, 1193–1196. [CrossRef]
122. Tanaka, Y.; Ishii, K.; Sawada, T.; Ohtsuki, Y.; Hoshino, H.; Yanagihara, R.; Miyoshi, I. Prophylaxis against a Melanesian variant of human T-lymphotropic virus type I (HTLV-I) in rabbits using HTLV-I immune globulin from asymptomatically infected Japanese carriers. *Blood* **1993**, *82*, 3664–3667. [CrossRef]
123. Suehiro, Y.; Hasegawa, A.; Iino, T.; Sasada, A.; Watanabe, N.; Matsuoka, M.; Takamori, A.; Tanosaki, R.; Utsunomiya, A.; Choi, I.; et al. Clinical outcomes of a novel therapeutic vaccine with Tax peptide-pulsed dendritic cells for adult T cell leukaemia/lymphoma in a pilot study. *Br. J. Haematol.* **2015**, *169*, 356–367. [CrossRef]
124. Kannagi, M.; Hasegawa, A.; Nagano, Y.; Kimpara, S.; Suehiro, Y. Impact of host immunity on HTLV-1 pathogenesis: Potential of Tax-targeted immunotherapy against ATL. *Retrovirology* **2019**, *16*, 23. [CrossRef]
125. Ratner, L. A role for an HTLV-1 vaccine? *Front. Immunol.* **2022**, *13*, 953650. [CrossRef]
126. UK National Screening Committee. Antenatal Screening for HTLV Infection. 2017. Available online: https://legacyscreening.phe.org.uk/policydb_download.php?doc=704 (accessed on 28 August 2019).
127. Satake, M.; Yamaguchi, K.; Tadokoro, K. Current prevalence of HTLV-1 in Japan as determined by screening of blood donors. *J. Med. Virol.* **2012**, *84*, 327–335. [CrossRef]
128. Willems, L.; Hasegawa, H.; Accolla, R.; Bangham, C.; Bazarbachi, A.; Bertazzoni, U.; de Freitas Carneiro-Proietti, A.B.; Hua Cheng, H.; Chieco-Bianchi, L.; Ciminale, V.; et al. Reducing the global burden of HTLV-1 infection: An agenda for research and action. *Antiviral. Res.* **2017**, *137*, 41–48. [CrossRef] [PubMed]
129. Okuma, K.; Kuramitsu, M.; Niwa, T.; Taniguchi, T.; Masaki, Y.; Ueda, G.; Sobata, R.; Sagara, Y.; Nakamura, H.; Satake, M.; et al. Establishment of a novel diagnostic test algorithm for human T-cell leukemia virus type 1 infection with line immunoassay replacement of western blotting: A collaborative study for performance evaluation of diagnostic assays in Japan. *Retrovirology* **2020**, *17*, 26. [CrossRef] [PubMed]
130. Kouseioudousyo. HTLV-1 Boshikannsennyoboutaisaku Manyuaru (Dai 2han). Available online: https://www.mhlw.go.jp/bunya/kodomo/boshi-hoken16/dl/06.pdf (accessed on 27 March 2023).
131. Shamir, R. The Benefits of Breast Feeding. *Nestle Nutr. Inst. Workshop Ser.* **2016**, *86*, 67–76. [PubMed]
132. Dias, C.C.; Figueiredo, B. Breastfeeding and depression: A systematic review of the literature. *J. Affect Disord.* **2015**, *171*, 142–154. [CrossRef] [PubMed]
133. Varandas, C.M.N.; da Silva, J.L.S.; Primo, J.R.L.; de Oliveira, M.d.F.S.P.; Moreno-Carvalho, O.; Farre, L.; Bittencourt, A. Early Juvenile Human T-cell Lymphotropic Virus Type-1–Associated Myelopathy/Tropical Spastic Paraparesis: Study of 25 Patients. *Clin. Infect. Dis.* **2018**, *67*, 1427–1433. [CrossRef] [PubMed]
134. Oliveira, P.D.; Kachimarek, A.C.; Bittencourt, A.L. Early Onset of HTLV-1 Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP) and Adult T-cell Leukemia/Lymphoma (ATL): Systematic Search and Review. *J. Trop Pediatr.* **2018**, *64*, 151–161. [CrossRef] [PubMed]
135. Schwalb, A.; Pérez-Muto, V.; Cachay, R.; Tipismana, M.; Álvarez, C.; Mejía, F.; González-Lagos, E.; Gotuzzo, E. Early-Onset HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis. *Pathogens* **2020**, *9*, 450. [CrossRef]

136. Yoshida, Y.; Sakamoto, Y.; Yoshimine, A.; Maruyama, Y.; Ikegami, N.; Inose, M.; Imamura, H.; Nakahara, K.; Nakagawa, M.; Osame, M. Three cases of juvenile onset HTLV-I-associated myelopathy with pseudohypoparathyroidism. *J. Neurol. Sci.* **1993**, *118*, 145–149. [CrossRef]
137. Gonçalves, D.U.; Proietti, F.A.; Ribas, J.G.R.; Araújo, M.G.; Pinheiro, S.R.; Guedes, A.C.; Carneiro-Proietti, A.B.F. Epidemiology, treatment, and prevention of human T-cell leukemia virus type 1-associated diseases. *Clin. Microbiol. Rev.* **2010**, *23*, 577–589. [CrossRef] [PubMed]
138. Maloney, E.M.; Yamano, Y.; Vanveldhuisen, P.C.; Sawada, T.; Kim, N.; Cranston, B.; Hanchard, B.; Jacobson, S.; Hisada, M. Natural history of viral markers in children infected with human T lymphotropic virus type I in Jamaica. *J. Infect. Dis.* **2006**, *194*, 552–560. [CrossRef] [PubMed]